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SOME HISTORICAL ASPECTS OF SMALLPOX.[1]

By FRANK S. HONE, B.A., M.B., B.S.,
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I CANNOT hope to make this subject as interesting to hearers as to myself, for in others that factor of personal experience which has directed my attention to the matter is absent, and they may wonder, as I should have done thirty years ago, why time should be wasted on this subject. Let me confess at once then that for me to write at all on this subject, and especially in my first paper before this historical section, is an ironical jest of fate. For, as a youth, I unconsciously absorbed the opinion that smallpox had been conquered by the discovery of vaccination and its compulsory enforcement. As a medical student at the Adelaide University I wondered why so much attention should be paid to smallpox in our lectures, to questions of diagnosis, when we were never likely to meet with it in our practice. For in those days our community in this State was isolated and protected from smallpox invasion, alike by the quarantine service of each State and by vaccination of a fair proportion (from a third to a half) of the community. There had been a small and localized outbreak at Bordertown in 1884, on which our President, Dr. A. A. Lendon, had been sent to report, but this, like other attempted invasions, had been immediately repelled. The wave of smallpox had almost inundated the Old World almost a century before, but here we only seemed to hear "its melancholy, long, withdrawing roar". That there was some excuse for this attitude is borne out by the statement in Dr. Cumpston's "History of Smallpox in Australia", written in 1908, in which he said:

[1] Read at a meeting of the Historical Section of the South Australian Branch of the British Medical Association on March 17, 1932.

"It is clear that South Australia has never had to record a serious epidemic of the disease."

The impression thus gained as a youth and a student was, if anything, strengthened by the first years of practice spent in a country district. At this time the introduction of glycerinated calf lymph apparently removed the last objection to vaccination, and the increasing interest of the community in public health culminated in the passage of the *Public Health Act*, 1898. Thus we appeared to have both the machinery and the public interest necessary to keep the community free from even a threat of an outbreak. And in the first few years of this century my practice in the district surrounding our chief seaport revealed nothing to weaken that impression.

Then in a curious way the situation and my personal relationships to it both changed. The Federal Committee came into existence in 1912, and as the Branch representative, travelling to and from Sydney in July, 1913, just when the epidemic of mild smallpox (or alastrim)—a disease hitherto unknown here—was exercising administrative minds in the eastern States, I was brought into close contact with the inconveniences one could suffer and the panic that could arise when smallpox gained a footing in the community. Dr. Gething's absence from this State a few months later, when suspected cases were thought to be occurring in this State and patients were sent to the Quarantine Station, showed me the easily made errors in diagnosis. The accidental landing of a patient with smallpox from South Africa whom I saw at Christmas, 1914, brought up the likelihood of diagnosis being required at any minute. Later Dr. Gething's death and my temporary assumption of the duties of Chief Quarantine Officer brought me into personal contact with administrative problems and the steadily increasing danger arising from the community's neglect of vaccination and our nearness to Eastern Asia. Later, Dr. Borthwick's refusal to assume the Lectureship in Preventive Medicine when it was established ten years ago, necessitated my keeping in touch with the changing aspects of the smallpox problem. There is no advocate like the convert; hence perhaps my interest has been greater than that of most of our members.

Apart from this personal interest, it has occurred to me that a brief historical survey of smallpox is interesting, as showing in a very special way the rise and fall in the incidence of an infectious disease, the problems presented to successive generations of our predecessors and their attempts at solution. In this respect smallpox serves as a good introduction to the historical study of other diseases, alike by comparison and contrast. The problems at first were those of differentiation, identification and nomenclature, then of treatment, and then of prevention; their setting and their extent changing from time to time as new factors were introduced by external conditions changing through commerce, politics or discoveries. With such an historical background to our thinking, we ourselves may possibly be able to adjust our minds better to those problems which may beset us in the near future, and thus, like the truly great, make "the present with the future merge, gently and peacefully, as wave with wave".

The subject of smallpox lends itself to this historical method of approach, for if we regard its history up to the end of the sixteenth century as one period, each century since is marked by some special feature of interest, and there are already indications that the present century in its turn will set special problems for us and our successors.

First Period.

The first period runs from the dawn of history to the end of the sixteenth century, by which time the disease had gradually spread over Europe and the New World.

The origin of the disease is lost in antiquity. Sir Armand Ruffer describes an eruption resembling smallpox in a mummy of the twenty-first dynasty, that is, about 1000 B.C., and the disease is said to be described in an Irish record of A.D. 675. But such stray references, repeated in text book after text book, are not convincing. A survey of records leaves a strong impression that, like bubonic plague, cholera and other virulent pestilences, smallpox had its original home in Central Asia, whence it has gradually spread both east and west by the agencies of armies and commerce. Thus Chinese records trace it in China to about A.D. 25 and say that it was imported from Central Asia. The earliest Chinese work on smallpox, dated 1323, states that inoculation had been practised since A.D. 960.

On the other hand, the oldest Japanese work written in 982 describes isolation hospitals for smallpox; which suggests that the need had existed for some time. Also, at this time the Japanese were already using red hangings in the treatment of the disease, which in England at quite a recent date was vaunted as a new discovery for the lessening of the secondary fever.

There is nothing resembling smallpox described in classical Greek writers on medicine. The historian Eusebius described a Syrian epidemic in A.D. 302; in A.D. 569 there is an account of its appearance in epidemic form at the siege of Mecca. Gregory, of Tours, mentions it in France in 586. These and other facts suggest an epidemic spreading westward during these years. The first good description of the disease is given by Rhagis, a famous Saracen clinician, about A.D. 900. Persian writers describe it about the same time and call it variola, a name that had been attached to the disease in 570 by Marius, Bishop of Avenches, when, as we saw above, it invaded France.

By A.D. 1000, then, smallpox would appear to have become endemic in Western Asia and to be brought into Europe about this time by the Saracens, and subsequently by returning Crusaders. It took another 600 years to entrench itself firmly in Western Europe.

Turning to English history, we find only scanty reference to the disease until the sixteenth century. Apparently it reached England about the end of the ninth century, all Europe being said to have been infected in the eighth century, apparently by the Saracens. Gilbertus Anglicus, the leading exponent of Anglo-Norman medicine, who died in 1252, was the first English writer to refer to it, but whether he had first hand knowledge of smallpox is uncertain. For he was a colossal reader and had studied in his youth at Salerno, in Italy, then the leading European medical school, where there was a library with all the Saracen literature. It is noteworthy that he refers to it as a contagious disease, and its possible conveyance by what he describes as "fumes" of the sufferer, although four hundred years later so great a physician as Sydenham maintained the contrary.

Gilbertus was succeeded by John of Gaddesden, who lived from 1280 to 1361 and was a prebendary of Saint Paul's, and is thought by some to be the original of Chaucer's "Doctor of Physic". He describes the disease in a medical compendium he had compiled, called "Rosa Anglica". He was employed as a physician by Edward II, and when one of the royal family fell ill, he wrapped the patient in a scarlet cloth and confined him in a bedroom hung with scarlet curtains and cured him "without a trace of scarring". Otherwise English historians of the fourteenth and fifteenth centuries are silent. It must be confessed also that all descriptions up to this time are vague, and it has been questioned whether they may not refer to *impetigo contagiosa* or to chicken pox. At first sight this may seem improbable, until we remember that so recently as 1884, Dr. A. A. Lendon, the President of this Section, who had then but recently arrived from England, was sent to investigate an outbreak of disease at Bordertown, which he proved to be smallpox. In a paper read subsequently to the South Australian Branch of the British Medical Association, after expressing his surprise that there had been any question of the disease being chicken pox, he said that Dr. Whittell, then President of the Central Board of Health, had informed him "that in these colonies the laity and many of the profession use the term chicken pox to denote vaguely any form of pustular eruption which is not smallpox, and that when they designate a disease chicken pox, they do not necessarily mean a true varicella and, moreover, that they often use the term 'native-pox' in precisely the same sense. The cases of so-called 'native-pox' which Dr. Whittell has seen and which were not chicken pox, appeared to him to closely resemble *impetigo contagiosa*". Australian medical literature before and about this time abounded in illustration of this loose use of terms.

The changes in nomenclature during the period up to the sixteenth century are also of interest. The name "variola" was given to the disease by Bishop Marius, of Avenches, when he described the epidemic of A.D. 570. But authorities differ as to the derivation of the term. The article in the "Encyclopædia Britannica" derives it from *varus*, a pimple, but other authorities (for example, Creighton and Webster's Dictionary) ascribe it to *varius*, meaning different, either (i) because of the different kinds of "pock" on the same body, or (ii) because of the different colours of the eruption. This Latin term was naturally used in medical writings. In old English "blain", "blotches" and "pocks" were the terms used to describe bodily eruptions. A "pock" was usually a pustule (possibly akin to pocket), and thus any pustular disease was called the "pocks". Hence the term cowpox, sheeppocks and chicken pox. It will be remembered that in the sixteenth century syphilis spread rapidly through Europe in epidemic form. It gradually became known as "the great pox" or the "pox". As it was gradually recognized that this was connected with sexual irregularities, it was necessary to protect victims of variola from the imputation that arose if they were said in the vernacular to be suffering from "the pox". Hence theirs was called smallpox to distinguish it from the "great pox". In 1614, for instance, which was looked upon as one of the worst years up to that time as regards the prevalence of smallpox in Europe and the East, the Duke of Buckingham, the court favourite, was ill, with what was generally accepted as syphilis, but a letter from a friend said: "He hath been crazy of late, not without suspicions of the smallpox." Creighton remarks that "the suggestion of smallpox appears to be the same euphemism which was resorted to in the cases of other exalted persons".

On the other hand, Creighton points out that early in the sixteenth century, when we meet with the first distinctive references to smallpox in England, the remarks to be made on the early uses are:

> First, that the word "*poques*" as used by one writing in French from London in 1514, did not mean smallpox, but pox; second, that the first authentic mention of smallpox happens to be in the French form, "*une maladie nommée la petite verolle*"; third, that in the political gossip of the time the opinion of the physicians regarding the illness of the young king is given as of a fever which they feared might have turned to the pustules called "variolæ"; and, fourthly, that in the first mention of the disease variola by an English name, "small pokkes", the name is modelled on the French, being coupled with the old English name "mezils".
>
> It is impossible to infer from these references anything as to the amount of smallpox in England at that time, or even to be sure of the correctness of the diagnosis. The lax usage as between "pox" and "smallpox" is shown in a book of the year 1530, called "Prognosticacions out of Ipocras and Avicien", in which a brief reference to "variola" in the Latin original is translated to "prognosticate of the pockes". In Sir Thomas Elyot's "Castel of Health", published in 1541, children after their first infancy are said to suffer from a number of maladies, and in "England commonly purpyls, meazles and smallpockes". That is perhaps the first use of the term in a systematic work on medicine, not indeed by one of the faculty, but by a layman.

This tendency to diminutives in naming a disease is widespread in medicine. Just as smallpox is a diminutive of great pox, so varicella is a diminutive of variola. The original name given to measles was morbilli or the little sickness, to distinguish it from

the true *morbus*, which was variola. Thus Rhagis wrote of variola and morbilli. In its turn, from the name rubeola, applied to measles, sprang the term rubella when the milder German measles was differentiated. We see the same tendency in the introduction of the terms congestion of the lungs and scarlatina.

In marked contrast to the occasional and scanty references to variola or smallpox in English writings up to the middle of the sixteenth century are the frequent references to it throughout the seventeenth century. It is evident that in the sixteenth and seventeenth centuries its westward march was not only accelerated and extended to America, but that it became endemic in countries where apparently it had only appeared spasmodically before in an occasional epidemic form. It is hard to account for this change. Buck says that it spread but slowly in ancient times from Egypt and Syria because of the slowness and infrequency of travel. Travel certainly became more widespread with the discovery of America and of the route to the East by the Cape of Good Hope. And armies tramped to and fro at this time over Europe and played a large part in the spread of syphilis. But there had been the same tramp of armies in the past centuries: with the invasion of Europe by the Saracens from the south in the ninth and tenth centuries and the East in the fifteenth century; with the return of the Crusaders from time to time during these centuries; with the English wars in France in the twelfth and thirteenth centuries. And it is doubtful whether, until the invention of steam transport, travel from one end of Europe to the other had ever been as rapid as it was in the best days of the Roman Empire. One can but suppose that with the stimulus to commerce which we know arose after the opening up of sea routes to the East and West Indies, there was a more general movement of peoples through commerce and thus a more ready means of exchange of diseases as well as merchandise.

At any rate, in 1517 the disease was carried from Spain to Santo Domingo and thence three years later to Mexico, where 3,500,000 natives died. From Mexico it spread over North America, and in the following years it is estimated that six millions out of the total population of twelve million Red Indians died of the disease.

The Seventeenth Century.

Thus, by the time the *Mayflower* pilgrims from England landed in America, the native tribes had been much weakened in numbers, so that Cotton Mather wrote: "The woods were almost clear of these pernicious creatures to make room for better growth". During the next hundred years six epidemics occurred in Boston, the last of these in 1721, from a case imported on an English ship, as a result of which half the population of Boston, which then numbered 11,000, contracted the disease. It had reached Pennsylvania in 1681 and Charleston in 1699.

In Europe itself the seventeenth century was the period in which the disease first assumed alarming proportions. There was an outbreak in Aberdeen in 1610 and a pandemic throughout Europe in 1614, and according to Creighton, the first true epidemic in London occurred in 1628. This epidemic made a great impression and from that time onwards weekly mortality bills were published in London, so that we have accurate record of the deaths from this disease. It was epidemic at intervals from 1661 to 1675, and it was about this time that Sydenham wrote his masterly description of measles as a separate disease. To us it may seem strange that it is only two hundred and fifty years since these two diseases were separated, especially as they had been separately described, as we have seen, by the Arabian physicians of the tenth century. But it is true, as has been seen in discussing nomenclature, that in Europe, up to the time of Sydenham, there was no clear differentiation between measles and smallpox, and this must be remembered in discussing all records of those times.

The position in England up to this time is admirably summarized by Creighton:

> History in Britain is that of a disease gradually coming into prominence and hardly attaining a landing place until the reign of James I. In this respect it is unlike plague and sweating sickness, both of which burst on the country in their full strength just as both made their first show in severe epidemics. Smallpox in the first Tudor reigns was usually coupled with measles; in Elizabeth's reign variolæ was rendered by measles and smallpox when distinguished from measles was not reputed as formidable. From the beginning of the Stuart period smallpox is mentioned in letters, especially from London, in such a way as to give the impression of something which, if not new, was at any rate much more formidable than before, and that impression is deepened by all that is known of the disease later in the seventeenth century.

The Eighteenth Century.

The eighteenth century is famous as the period of the maximum devastation of Europe and England by smallpox. During the whole of this time it was endemic or epidemic in England and caused great mortality, so that public dread of the disease became more and more marked. The way had been paved for this wave of terror at the end of the seventeenth century by two sons of James II being attacked and by the illness and death from smallpox of Mary in 1694. Macaulay's famous and oft quoted passage, written, of course, over one hundred years later, says:

> This disease, over which science has achieved a succession of glorious and beneficent victories, was then the most terrible of all the ministers of death. The havoc of the plague had been far more rapid; but the plague had visited our shores only once or twice within living memory; and the smallpox was always present, filling the churchyard with corpses, tormenting with constant fears all whom it had not yet stricken, leaving on those whose lives it spared, the hideous traces of its power, turning the babe into a changeling at which the mother shuddered, and making the eyes and the cheeks of the betrothed maiden objects of horror to the lover. Towards the end of the year 1694 this pestilence was more than usually severe. At length the infection spread to the palace and reached the young and blooming queen.

Although written at the beginning of the nineteenth century, this reflects the popular outlook on

the disease at that time as the result of events in the century following Queen Mary's death.

It is generally agreed now that Macaulay's statement is exaggerated and some writers even say that it is difficult to decide whether the disease was really more extensive or that more attention was focused on it. It is true that from the time of Sydenham we enter on a different phase of medicine, when observation replaced theory. The causes of death were better recorded, also that we have actual records. None the less, the figures emphasize the much greater prevalence of the disease. Rosenau says that it is estimated that sixty millions of people died of smallpox alone in Europe within the eighteenth century; that a French physician stated that every tenth death was due to smallpox and that one-quarter of mankind was either killed by it or crippled or disfigured for life; that in Italy in that century 90% of the population suffered from smallpox.

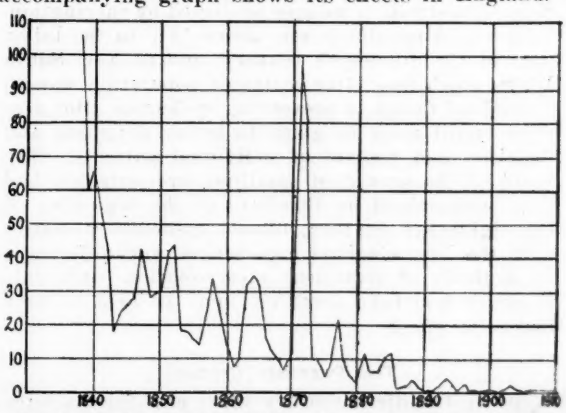
Similarly in England there were great epidemics at intervals, the exact period varying in different parts of the country. One of the greatest occurred in 1710 and the years 1740 to 1742 were years of widespread epidemics. These were years of distress and typhus fever which aggravated the position. The first smallpox hospital in London was opened in 1746. Some writers call this the first in the world, but as we have seen, Japan had them 800 years previously.

A few instances illustrate the common experience. In 1722, in Ware, a town with a population of 2,515, at the end of the epidemic there were only 302 who had never had the disease and these were described "to have the disease". In Chester, in 1755, out of 15,000 inhabitants only 1,060 had not had smallpox at some time. In other towns it was reckoned that out of every 1,000 babies 161 died of smallpox in infancy; for it must be remembered that in those days smallpox was a disease of infancy and young childhood.

The eighteenth century is also distinguished by the first attempt to introduce preventive measures on a large scale. All are familiar with the story of Lady Wortley Montague who was so impressed by the apparent advantages of this measure in lessening mortality in the East, that she had her eldest son inoculated in Constantinople in 1717 and subsequently in 1718 wished to have her younger son similarly treated in England. Her determined and persistent advocacy popularized the measure. For the next few years the method was followed which she had introduced—a sufferer from a mild form of the disease was selected, the individual to be inoculated had his skin punctured and the variolous matter was introduced. After some years this method fell into disrepute because several notable people died as the result, and from 1721 to 1743 a modified measure was used by which an incision was made in the skin and lint soaked in variolous matter was introduced. This method gave more pustules. In the meanwhile the method had spread to New England, being first used in the Boston epidemic of 1721 where further modifications were introduced, and about 1740 one of these was brought back to England, called the Suttonian method. In this method, in order to overcome the too numerous fatalities, the variolous matter used was from an immature pustule, the aim being to reduce the reaction as much as possible, and only produce a few pustules. Here we have the forerunner of modern surgical experience, as the second half of the eighteenth century saw as many modifications of inoculation put forward in America and England as we have seen in recent days in regard to operations for replacement of the uterus. Inoculation hospitals were opened, practical experiments made with animals and condemned criminals to determine the safety and the efficiency of the method. Most of these were useless, as many of the individuals had probably had the disease in childhood and were already protected, while failures would not come to light, as the persons passed on to other districts before they contracted the disease. The Suttonian and similar methods were safer, but did they protect, when the reaction was so attenuated? It is generally agreed now that all attempts to estimate the total advantages of inoculation contained sources of fallacy, and to the end of the eighteenth century, when Jenner's method of inoculation was discovered, it was an open question whether inoculation did not do more harm by spreading the disease than it did good in lessening deaths.

The Nineteenth Century.

The beginning of the nineteenth century saw the beginning of the crusade for Jenner's method of vaccination by lymph modified through transmission through the cow, its gradual acceptance as a valued method of community protection, and its increasing triumphs—most clearly demonstrated in pre-war Germany, where compulsory vaccination in infancy and revaccination in adolescence made smallpox an unknown disease, except for odd introduced cases near the border. The story of vaccination is so well known that I can pass it over, but the accompanying graph shows its effects in England.



Graph showing English death rate from smallpox since 1838. Note: Vaccination from 1854 to 1872 was obligatory but not enforced. It was enforced from 1872. Before this epidemics occurred every five years with an occasional tidal wave. (After Hewlett and Nankivell.)

Comparison of its success in gradually stamping out the disease in England with the figures quoted above for the eighteenth century raises an interesting question. The population of England and Wales in 1400 was estimated at about two and a half millions. By 1500 it was estimated at four and three-quarter millions, or nearly double. We have seen that the next century saw the beginning of the increased incidence of smallpox, which culminated in the eighteenth century. From 1500 to 1800 the population grew only from nearly five to nine millions—nearly doubled in three centuries. By 1900 it was up to thirty-two and a half millions. Making all allowances for improved industrial and living conditions, we wonder how much of this sudden change was due to check of smallpox mortality.

The nineteenth century was notable also from our point of view because, for the first time, Australia came into the historical picture. Although the records are scanty in the early days of colonization, there is evidence of three distinct outbreaks of smallpox among the aboriginal population up to 1850, one corresponding with the first advent of the white settlers, the second in 1830, and the third later. The exact mode of introduction is uncertain, but each caused heavy mortality amongst the natives. Yet in contrast to American experiences in the seventeenth and eighteenth centuries, only isolated instances occurred of infection of white settlers; and although during the hundred years subsequently smallpox has again and again reached our shores, in most cases it has been stopped at the threshold by effective quarantine administration, and where it has slipped through, no large epidemic has occurred, such as that mentioned in Boston in 1721.

The explanation of this is somewhat uncertain. It cannot altogether be put down to vaccination, for that was little practised in the first half of the century. By the middle of the century most of the States were enacting compulsory vaccinations. The first Act in South Australia was in 1853. But New South Wales has never made it compulsory. It is estimated that at the most only 30% of the population of Australia were ever protected by vaccination. In South Australia it was about 54% in the latter part of the nineteenth century, and in New South Wales much less. Our scattered population was an undoubted factor in preventing epidemics. But also some credit must be given to better diagnosis and isolation and control of individual patients. The truth of the spread of smallpox by contagion had first been proved by Boerhave at the beginning of the eighteenth century, almost contemporaneously with the New England experiences, and differences in methods of treatment and isolation, once this principle had been accepted, must be held to have had some effect.

The Twentieth Century.

In the twentieth century three new factors have appeared:

1. The first is the appearance of the mild form of smallpox on a world-wide scale. Vaughan and other epidemiologists say that the original habitat of this is in Africa, where it is known as Amaas or Kaffir milk fever—that it is in fact the African form of smallpox, just as the familiar form known previously in Europe was the Asiatic form. This mild form first came into public notice in Trinidad and the West Indies towards the end of the last century, where it was called "alastrim". It was imported into the United States of America by the troops returning from Cuba after the Spanish-American war, and was known as the "Cuban itch". It spread across the continent to San Francisco, from there to New Zealand in 1912, and made its appearance in Australia in the famous New South Wales epidemic in 1913.

In 1914 we had it imported into South Australia from Africa by a patient on the *Runic*, but it was stopped at the seafront. It appeared in England about ten years ago and, as all know, has been there in epidemic form ever since, escaping to Australia by the *Barrabool* in 1927, but being again checked at the port of entry. Its mortality is practically nil, and although there have been fears constantly expressed of its suddenly assuming a virulent form, both in Canada and Great Britain the two forms occur side by side, each maintaining its respective form of virulence. This differentiation of the mild and severe form of smallpox is typical of what is going on in other diseases in the twentieth century, as, for example, in typhoid and paratyphoid fever (although in these separate causal organisms have been established) and in the mild endemic typhus as distinguished from the severe epidemic typhus (although different methods of conveyance have been proved for these two diseases).

2. Apart from the difficulty of diagnosis and administration raised by the spread of this mild form, it is important because of its bearing on the question of vaccination. In Australia compulsory vaccination has almost become a dead letter, largely from the public, as a whole, feeling secure from invasion. In England the position has been complicated by the occurrence of a fair number of cases of encephalitis after vaccination, and this development, occurring at the same time as the epidemic of mild smallpox, an attack of which protects equally with vaccination, has thrown the whole question of vaccination into the melting pot. The result is that at a discussion at the Royal Society of Medicine about three years ago, quite a number of speakers questioned the wisdom of continuing the present system. In this respect also smallpox is facing the same question as other diseases in the twentieth century. So long as vaccination against smallpox was the only form of preventive immunization and smallpox was dreaded beyond all other diseases, no difficulties arose. But with the discovery of similar successful methods against typhoid, scarlet fever, diphtheria and so on, some common method of procedure regarding immunization against all these diseases comes under discussion. And with diphtheria, as with smallpox, we have seen in recent years the accidents that may befall attempts at routine community immunization.

3. The third new factor which especially affects Australia, is the spread of aviation. Quarantine against smallpox importation from the East last century was possible, because to reach Australia from the nearest port in Asia took a longer period than the fourteen days' incubation period of smallpox. With the faster steam service of the past twenty years this period of time has been shortened; in the next twenty years it is evident that aviation will reduce it to three or four days, and our present system of quarantine will need to be modified to a system of inspection such as in England. And so, just as aviation has restored Bagdad and Damascus to that ancient importance which they lost with the advent of steamship travel, just as it again pushes into prominence the north of Australia compared with the south, so in regard to conveyance of smallpox from Asia it puts Australia much where Eastern Europe was a thousand years ago.

Thus the two safeguards which Australia enjoyed last century from its unique quarantine service, which was possible owing to its isolation, and from the relative protection of its community by vaccination, are now being removed.

And this may be pleaded as the justification for this historical sketch to younger members who will have to deal with the new situation thus created.

THE SERUM TREATMENT OF EXPERIMENTAL STREPTOCOCCAL INFECTION.

By W. J. PENFOLD, M.B., Ch.M. (Edinburgh), D.P.H., B.Hyg. (Durham), M.R.C.S. (England), L.R.C.P. (London),

AND

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(*From the Baker Institute of Medical Research, Alfred Hospital, Melbourne.*)

PROFESSOR W. VON LINGELSHEIM,[1] writing as recently as 1928, states:

> Today even there are still hardly any reliable accounts of the therapeutic efficacy of the serum preparations obtainable on the market. Generally they are still regarded rather sceptically, which is not to be wondered at considering the difficulties just described in their production. Still, without doubt, many streptococcal diseases can, with early application, be favourably influenced by larger doses of this or that preparation.

How we are to identify in practice "this or that preparation" which can exert a favourable influence in any particular streptococcal infection is extremely difficult to say. It must be admitted with von Lingelsheim that there are still hardly any reliable criteria of the therapeutic efficiency of commercial streptococcal serum. We give in this paper an account of an attempt made to identify, by the use of a particular technique, the serum most suitable for individual cases about to be treated. We did not test the sera by determining their power curatively to neutralize experimental infections due to passage strains, a method which has been so much used by serum makers. Virulence for the rabbit or the mouse is of small interest to the medical bacteriologist if it has been conferred by artificial passage and does not characterize the strain in the patient's body. Inoculation with passage strains has been used by Aronson, Meyer, Ruppel and many others in serum production, followed sometimes by large quantities of streptococci recently isolated from man, but the sera so produced have not been found effective.

Tavel and Moser immunized with as many strains as possible, the strains having been obtained immediately beforehand from the human body. The horses, during immunization, became anaphylactic and the human strains were so slightly virulent as to make tests in small laboratory animals difficult.

Meyer and Ruppel also tried to produce immunity by the use of passage strains followed by strains that showed, as they came from the human subject, virulence for small laboratory animals. Polyvalency and natural virulence in addition to passage virulence were the guiding ideas of their work.

The grouping of streptococci on morphological, biological and serological lines has caused the immunization of horses by representative type strains to be undertaken. The sera so produced have been mixed and used therapeutically. When no benefit has resulted, it has been held that the infecting strain was substantially different from any used in the production of the serum.

Meyer and Joseph[2] considered that a general streptococcal infection was preceded by an initial intoxication. They held the toxin to be qualitatively similar in the case of all streptococci. This toxin was a hæmotoxin, which they did not find very toxic for small animals. It produced, however, according to their work, toxic effects in horses and in them gave rise to antitoxin. In addition to the use of this hæmotoxin, large quantities of living streptococci recently isolated from human sources were also inoculated into the horses, representative strains of various groups being used.

Various workers[3] on hæmotoxins produced by streptococci have not succeeded in getting a good antitoxin in the small laboratory animals in which the experiments were tried.

Much recent work has been directed to the study of the Dicks'[4][5][6] skin toxin produced by hæmolytic streptococci. While an efficient antitoxin can be produced to the Dick toxin, it seems very doubtful if this toxin alone ever causes death in man. From work done in rabbits, however, Parish and Okell[7] have shown that enormous doses of the toxin may be fatal and have come to the conclusion that this toxin has the power, when administered with culture, of determining acute fatal streptococcal infection, while, if antitoxin be given previously to or simultaneously with the culture, the majority of the rabbits so treated survive during their observation period (six days). These surviving animals, however, show chronic infections, especially arthritis, pericarditis and other complications. The outcome of these infections is not fully dealt

with by the authors. The toxin which Parish and Okell used, was extremely weak, 20 to 40 cubic centimetres being required to produce a fatal result in rabbits of medium weight, while the broth from which the toxin was made was shown by them not to be fatal in doses of 53 cubic centimetres. In testing their sera whole broth culture was used in doses of 10 cubic centimetres. What fraction of a lethal dose of toxin was present in these 10 cubic centimetres cannot be deduced from the data given, but, unless much of the toxin were lost in filtration, the dose is probably a sublethal one. Their work suggests, therefore, that this extremely weak toxin may be a factor in enabling the streptococcus to grow in the body and so produce a generalized infection. In their work no control inoculations were undertaken of the centrifuged organisms from 10 cubic centimetres of culture to which 10 cubic centimetres of the original broth had been added, though they admit that the broth in large doses does produce certain evanescent toxic results. The effect of the washed organisms alone in the production of acute septicæmia is not dealt with. It is shown, however, that the serum produced from the inoculation of such washed organisms will not prevent the acute septicæmia.

These results of Parish and Okell suggested the possibility that scarlet fever antitoxic serum might be generally useful in preventing early death in hæmolytic streptococcal septicæmia. Consequently, scarlet fever antitoxin was one of the sera brought under test. Parish and Okell attribute no effect to possible antihæmotoxin in their serum, though, as we have seen, Meyer and Joseph ascribe an important rôle to it. Assuming that each of these streptococcal toxins has the rôle suggested and that it can produce an antibody in the horse, then it would seem desirable to select from the available commercial sera those that were most capable of preventing early death in animals experimentally infected with the patient's own strain. In the case of Parish and Okell's rabbits, each given a standard dose of 10 cubic centimetres of broth culture, 86% of them were dead by the third day and 78% on the second, so that even on the second day an opinion as to the value of a serum might be obtained by the use of their statistical method.

It was not possible for us to work precisely on their lines in a clinical research. Rabbits were too expensive, especially in the large numbers they used. The mouse, therefore, was chosen as a cheap substitute in which our inquiry could be conducted with possible benefit to the patient.

Lancefield, Todd and Andrews have shown that in the case of the streptococci, as in that of other organisms, the character of the colony may give fairly reliable information as to virulence. Lancefield and Todd describe mat and glossy colonies. The mat colonies were obtained by mouse passage of old cultures of relatively low virulence and by colony selection. They obtained the glossy from the mat types by growing the latter in a serum produced by injecting mat organisms into suitable animals. After prolonged growth in such a serum, by colony selection the glossy strains were obtained. It was difficult to get absolutely pure strains of the glossy type, and a considerable amount of attenuation of the mat strains could be obtained before the colonies lost entirely their mat character. Lancefield and Todd attach little importance to antitoxin in the control of the experimental infections they studied. The mat strains are the most virulent, produce better immune serum and usually better vaccines, but since the virulence here dealt with is mouse virulence, it seems that much of this work is closely related to earlier work on streptococcal immunization where passage strains were used as indicated in the opening paragraphs of this paper. Lancefield and Todd illustrated the specificity of the protection they obtained, but it is questionable whether any very important advance in serum making has as yet resulted from their work. The specific immunization of the patient against the specific streptococcus infecting him remains an extremely difficult problem for the practical physician.

Denys and Bordet have shown that phagocytosis plays an important part in streptococcal immunity, and Neufeld believes this is largely due to the tropin content of the serum. Even when the tropin content of the serum is small, a considerable degree of protection may be present in the animal, believed to be due to some form of cellular immunity affecting especially the reticulo-endothelial system. The titration of specific tropins is extremely difficult and has not been attempted in the standardization of commercial sera available in Australia.

The curious phenomenon called "depression immunity"[8] has been noted in streptococcal infections. If an animal already suffers from a streptococcal infection, a virulent new strain inoculated into the animal, from twenty-four hours to six days after the onset of the first infection, will not be able to produce an acute infection. This is not due to an immediate loss of virulence by the strain used for the second infection, for, on its being inoculated again into a normal animal, it is found to be fully virulent. The preexisting infection simply converts the new infection into a chronic one. This type of immunity has no practical application in the human subject.

The bactericidal effect of streptococcal serum is doubtful. Fresh serum has been claimed to possess bactericidal powers, and old serum, in the presence of complement, has been found bactericidal by some workers. Streptococci will grow in immune serum. To commence with it may have some hindering effect, but this is only temporary. In testing antistreptococcal immune serum in animals the following points should be attended to as far as possible.

The total amount of culture used should be small (Aronson). (It is apparently easier to phagocyte a small number of virulent organisms than a large number of slightly virulent ones.) Nevertheless it should contain a high multiple of the fatal dose of

the culture. Aronson recommended multiples of 100 to 1,000. In our work with the human strains we have not been able to fulfil these requirements, but we have approached them as closely as was possible in the circumstances.

The emulsion to be used should be uniform. A common practice is to give the serum subcutaneously twenty-four hours before administering the living culture, which is usually given intraperitoneally. This practice may be quite good when it is proposed to use the serum prophylactically, as in labour before the onset of possible septicæmia, but, when a serum has to be used therapeutically, very exaggerated notions of its value might be obtained in this way. In carrying out the titration, one may vary the dose of serum, keeping the bacteria constant, or the dose of bacteria, keeping the serum constant.

The animals are usually observed for a short specified time, maybe four, six or eight days. This method of observation takes no cognizance of late deaths, which cannot be ignored.

A certain amount of work has been done in estimating the therapeutic value of convalescent serum. Neufeld was not able to demonstrate its value, although tests were made against the strain isolated from the patient yielding the serum. Zangemeister, on the other hand, was able to protect mice by the use of convalescent serum. The possibility is that the immunity resulting from streptococcal infections is short-lived and the time of taking the serum may be very important. Its antibody content is liable to fall soon after the infection has passed.

Experimental Investigation.

The great bulk of the experiments recorded in this paper were conducted as follows:

The standard mouse weighed 25 grammes. The material injected was recently isolated cultures of the streptococci under examination, which had been grown in tryptic broth for exactly twenty-four hours. Half the culture was centrifuged and the deposit was used to make the remaining half up to 2,000,000,000 organisms per cubic centimetre. Three parts of this emulsion were mixed with two parts of serum and, immediately after mixing, half a cubic centimetre of the mixture was injected intraperitoneally into each mouse. The liquid portion of the broth, therefore, was present, and any toxin it might contain would be able to exert its influence.

A small group of experiments was done in which the organisms were centrifuged from the broth and suspended in saline solution, 2,000,000,000 to the cubic centimetre. In this case any exotoxin present would be minimal. In the experiments in which the saline emulsion of the bacteria was used, the serum was first injected intraperitoneally in 0·2 cubic centimetre quantity, and when all the doses of serum had been administered to the mice, they were then in turn given their doses of emulsion by the same route. Only a short interval elapsed between the two injections.

The strains were not found to be very virulent; 0·03 cubic centimetre of the emulsion could not be relied on as a fatal dose. The test dose was always 0·3 cubic centimetre of the emulsion and, therefore, frequently contained less than ten fatal doses. Owing to the low virulence of the organisms, we were obliged to use a fairly large number of bacteria and not a high multiple of the fatal dose. All injections were given intraperitoneally, as this method gives excellent results in testing pneumococcal sera. The animals were observed as a rule for six weeks so that cognizance would be taken of late deaths. The general results of the experiments are set out in the accompanying tables.

TABLE I.[1]

Case I: Cellulitis of Leg.

20/8/28. Pus cultured.
21/8/28. Found positive—hæmolytic streptococcus.
Virulence and protection tests carried out August 21, 1928, at 3.30 p.m.

No. of Mouse.	Dose Given.	Days of Observation.								
		1 22/8/28.	2	7	8	9	10	11	12	13
1	0·3 c.cm. Emulsion	+1 p.m.								
2		f.d. 9 a.m.								
3		f.d. 9 a.m.								
4		+ 4 p.m.								
5	0·03 c.cm. Emulsion	–	+							
6		–	–	+						
7		–	–	–	–	–	–	–	–	+
8		–	–	–	–	All	ve 6	at wk	end s	of
9	0·3 c.cm. Emulsion	f.d. 9 a.m.								
10		f.d. 9 a.m.								
11	+ 0·2 c.cm. N.H.S.	f.d. 9 a.m.								
12		–	+							
13	0·3 c.cm. Emulsion +	f.d. 9 a.m.								
14		+9 a.m.								
15	0·2 c.cm. Serum C.	+9 a.m.								
16		–	+							
17	0·3 c.cm. Emulsion +	f.d. 9 a.m.								
18		+12 noon								
19	0·2 c.cm. Serum C.P.	+3 p.m.								
20		–	+							

The sera which we submitted to test were prepared by British, American and Australian manufacturers of repute, who are designated in this paper by the letters A, B and C. Various batches were used from each manufacturer, and the work was controlled as adequately as possible in different directions. When two or more different types of antistreptococcal sera were issued by a maker, a distinctive letter was added to indicate the second or third type. The commercial sera tested all contained antiseptic. The amount in the mixture of serum and bacteria was not, however, sufficient to interfere with the virulence of the bacteria, as a glance at the tables will show. On the other hand, the amount of antiseptic present may be held to have injured the defensive mechanism of the body and so occasioned the many untoward results we have obtained. When testing pneumococcal serum with the same concentration of antiseptic present the results are satisfactory, and in the tests done with the majority of our own streptococcal strains the sera showed themselves innocuous in spite of the contained antiseptic. Since the antiseptic is present in the commercial serum, the clinical tests should, in our opinion, be done in its presence.

When the mice were about to be used for experimental purposes they were taken from a collection of about 1,000 to 1,500 normal mice, kept in an animal house at a constant temperature of about 21° C. Usually groups of four were placed in shallow, wide earthenware dishes, covered with metal gauze lids. A certain amount of cotton waste was provided in each dish to keep the animals warm. The food consisted of bread moistened with fresh milk, sunflower seeds and cabbage leaves. At first, when

[1] An explanation to the tables will be found on page 736.

TABLE II.

Case II.: Cellulitis of Leg.

16/8/28 Culture from blister.
17/8/28. Found positive—hæmolytic streptococcus.
Virulence and protection tests carried out on August 17, 1928, at 12 noon.

No. of Mouse.	Dose Given.	Days of Observation.								Remarks.
		1	2	3	4	5	6	7	8	
1	0·3 c.cm. Emulsion.	—	—	—	—	—	—	—	—	Alive at end of 6 weeks.
2		—	—	—	—	—	—	—	—	
3	0·03 c.cm. Emulsion.	—	—	—	—	—	—	—	—	Alive at end of 6 weeks.
4		—	—	—	—	—	—	—	—	
5	0·3 c.cm. Emulsion +	—	—	—	—	—	—	—	—	Alive at end of 6 weeks.
6	0·2 c.cm. N.H.S.	—	—	—	—	—	—	—	—	
7	0·3 c.cm. Emulsion +	—	—	—	—	—	—	—	—	Alive at end of 6 weeks.
8	0·2 c.cm. Serum C.	—	—	—	—	—	—	—	—	
9	0·3 c.cm. Emulsion +	—	—	—	—	—	—	—	—	Alive at end of 6 weeks.
10	0·2 c.cm. Serum C.P.	—	—	—	—	—	—	—	—	

these mice in the small groups of four were placed in their new environment, deaths were liable to occur due to sudden changes of temperature, but when the new room in which they were kept was closed up and heated with a radiator until the temperature was about 21° C., then no more deaths occurred than amongst the mice kept in the breeding pens. The room where these experimental mice were kept was found to be absolutely stuffy, nevertheless large numbers of mice used as controls of the effect of the environment could be kept for long periods with a negligible number of deaths.

Owing to the fact that the standard dose of bacteria was relatively large, killed bacteria were also injected into controls to see if the bacterial protein itself might be so toxic as to upset our results. (See Tables VI, VII, VIII, IX, where this was not found to be the case.) The effect of normal horse serum was used as a control in every experiment to ascertain what amount of any effect obtained was due to the specific character of the serum. The usual number of animals used to determine any effect was four. It must be admitted that a substantial variability of the animals does occur, but where experiments were repeated the results were essentially similar, so that it seems likely that four mice are usually enough to determine approximately any one point. In one case at least the repetition was on such a scale as to cut out the possibility of error from the small size of the samples used.

The value of a serum was determined by observing the survival period of the treated animals in comparison with that of the untreated ones. The survival time has been expressed in the paper variously; in the average number of days, if the survivors only lived a few days. A better method of expression, and the one most favoured in this paper, is the time taken for two out of the four animals to die. We designate it the 50% death time. The middle point

TABLE III.

Case III: Septicæmia.

22/10/28. Blood culture taken.
23/10/28. Found positive—hæmolytic streptococcus.
Virulence and protection tests carried out on October 24, 1928, at 12 noon.

No. of Mouse.	Dose Given.	Days of Observation.										Time Taken for Half the Animals to Die.
		1 25/10/28	2	3	4	5	6	7	8	9		
1	0·3 c.cm. Emulsion.	f.d. 9 a.m.										1 day.
2		—	—	—	—	—	+					
3		f.d. 9 a.m.										
4		—	—	—	—	—	—	—	—		Alive at end of 6 weeks.	
5	0·03 c.cm. Emulsion.	—	—	—	—	—	—	—	+			9 days.
6		—	—	—	—	—	—	—	—	+		
7		—	—	—	—	—	—	—	—	+		
8		—	—	—	—	—	—	—	—		Alive at end of 6 weeks.	
9	0·3 c.cm. Emulsion +	f.d. 9 a.m.										1 day.
10	0·2 c.cm. N.H.S.	f.d. 9 a.m.										
11		—	f.d. 9 a.m.									
12		—	f.d. 9 a.m.									
13	0·3 c.cm. Emulsion +	—	f.d. 9 a.m.									2 days.
14	0·2 c.cm. Serum C.	—	f.d. 9 a.m.									
15		—	—	—	—	—	—	+				
16		—	—	—	—	—	—	—	+			
17	0·3 c.cm. Emulsion +	f.d. 9 a.m.										1 day.
18	0·2 c.cm. Serum C.P.	f.d. 9 a.m.										
19		—	f.d. 9 a.m.									
20		—	—	—	+							

TABLE IV.

Case IV: Infected Hæmatoma of Scalp.

13/11/28. Pus cultured.
14/11/28. Found positive—hæmolytic streptococcus.
Virulence and protection tests carried out on November 15, 1928, at 11.30 a.m.

No. of Mouse.	Dose Given.	Days of Observation.									Average Time of Death.
		1 16/11/28	2	3	4	5	6	7	8		
1	0·3 c.cm. Emulsion.	+3 p.m.									3·25 days.
2		–	–	+							
3		–	–	–	+						
4		–	–	–	–	+					
5	0·03 c.cm. Emulsion.	–	–	–	–	+					——
6		–	–	–	–	–	–	–	+		
7		–	–	–	–	–	–	–	–	} Alive at end of 6 weeks.	
8		–	–	–	–	–	–	–	–		
9	0·3 c.cm. Emulsion +	–	f.d. 9 a.m.								3·5 days.
10	0·2 c.cm. N.H.S.	–	–	+							
11		–	–	–	+						
12		–	–	–	–	+					
13	0·3 c.cm. Emulsion +	–	f.d. 9 a.m.								2·75 days.
14	0·2 c.cm. Serum C.	–	f.d. 9 a.m.								
15		–	–	+							
16		–	–	–	+						
17	0·3 c.cm. Emulsion +	–	f.d. 9 a.m.								2·75 days.
18	0·2 c.cm. Serum C.P.	–	f.d. 9 a.m.								
19		–	–	+							
20		–	–	–	+						

of time between the deaths of the second and third animals would also be useful, but the third animal frequently did not die with the smaller of the two doses of emulsion tested. In these two latter ways, if a specially resistant animal were present in the four, the death time would not be materially affected. If, on the other hand, two highly susceptible mice were present in the four, then the death time would not give true results. This error may occasionally arise in our method of investigation, but we believe it to be infrequent. The death times recorded with 0·03 cubic centimetre doses of emulsion not infrequently enabled us to determine the number of 50% lethal doses that were given in 0·3 cubic centimetre, which was the standard test dose. As before mentioned, the middle point of

TABLE V

Case V: Septicæmia.

1/12/28. Blood culture taken.
2/12/28. Found positive—hæmolytic streptococcus.
Virulence and protection tests carried out on December 5, 1928, at 12 noon.

No. of Mouse.	Dose Given.	Days of Observation.									Average Time of Death.
		1 6/12/28	2	3	4	5	6	7	13	14	
1	0·3 c.cm. Emulsion.	+2 p.m.									2 days.
2		+6 p.m.									
3		–	f.d. 9 a.m.								
4		–	–	–	+						
5	0·03 c.cm. Emulsion.	–	–	–	+						——
6		–	–	–	–	–	–	–	–	+	
7		–	–	–	–	–	–	–	–	} Alive at end of 6 weeks.	
8		–	–	–	–	–	–	–	–		
9	0·3 c.cm. Emulsion +	f.d. 9 a.m.									2·25 days.
10	0·2 c.cm. N.H.S.	f.d. 9 a.m.									
11		–	–	–	+						
12		–	–	+							
13	0·3 c.cm. Emulsion +	+2 p.m.									2·25 days.
14	0·2 c.cm. Serum C.	–	f.d. 9 a.m.								
15		–	f.d. 9 a.m.								
16		–	–	–	+						
17	0·3 c.cm. Emulsion +	f.d. 9 a.m.									2·25 days.
18	0·2 c.cm. Serum C.P.	f.d. 9 a.m.									
19		–	f.d. 9 a.m.								
20		–	–	–	–	+					
21	0·3 c.cm. Emulsion +	–	–	–	+						5·5 days.
22	0·2 c.cm. Serum B.	–	–	–	+						
23		–	–	–	–	–	–	+			
24		–	–	–	–	–	–	+			
25	0·3 c.cm. Emulsion +	+5 p.m.									3·75 days.
26	0·2 c.cm. Serum A.U.	–	–	–	+						
27		–	–	–	–	+					
28		–	–	–	–	+					

TABLE Va.

Case V: Septicæmia.

Virulence and protection tests repeated on December 11, 1928, at 5 p.m.

No. of Mouse.	Dose Given.	Days of Observation.											Average Time of Death.
		1 12/12/28.	2	3	4	5	6	7	8	9	10		
1	0·3 c.cm. Emulsion.	–	f.d. 9 a.m.										2·5 days.
2		–	f.d. 9 a.m.										
3		–	–	+									
4		–	–	+									
5	0·03 c.cm. Emulsion	–	–	–	–	–	–	+					
6		–	–	–	–	–	–	–	–	–	–	Alive at end of 6 weeks.	
7		–	–	–	–	–	–	–	–	–	–		
8		–	–	–	–	–	–	–	–	–	–		
9	0·3 c.cm. Emulsion +	–	f.d. 9 a.m.										2·5 days.
10	0·2 c.cm. N.H.S.	–	f.d. 9 a.m.										
11		–	–	+									
12		–	–	+									
13	0·3 c.cm. Emulsion +	–	f.d. 9 a.m.										2·75 days.
14	0·2 c.cm. Serum C.	–	–	+									
15		–	–	+									
16		–	–	+									
17	0·3 c.cm. Emulsion +	f.d. 9 a.m.											2·25 days.
18	0·2 c.cm. Serum C.P.	f.d. 9 a.m.											
19		–	f.d. 9 a.m.										
20		–	–	–	–	+							
21	0·3 c.cm. Emulsion +	–	–	+									6·5 days.
22	0·2 c.cm. Serum B.	–	–	–	–	+							
23		–	–	–	–	–	–	–	+				
24		–	–	–	–	–	–	–	–	–	+		
25	0·3 c.cm. Emulsion +	–	–	+									4 days.
26	0·2 c.cm. Serum A.U.	–	–	+									
27		–	–	–	+								
28		–	–	–	–	–	+						

time between the deaths of the second and third mice may be taken as the middle or central death time and should be more accurate than the 50% death time, since it takes cognizance of the death times of both the second and third animals. In the case of a series having an odd number of animals, the middle or central death time would be the time of death of the middle animal of the series.

An unexpected result was very soon revealed by our experimental work, namely, the administration of serum was found quite frequently to shorten the lives of the animals. This shortening occurred sometimes also with normal serum, but usually not to the same degree. On the other hand, many of our infected animals were apparently not influenced at all by serum treatment; the results in the treated animals and in the untreated were substantially similar. In a few cases the specific serum seemed to be of definite value in the treatment of the experimental infection.

It is well recognized by authors dealing with the use of therapeutic streptococcal serum in man that the serum is very frequently useless, though, on the other hand, it may occasionally be followed by dramatic improvement. We have not met in the literature, however, any definite and convincing evidence that the use of the serum may be disastrous. As far as our experimental work in mice goes, it has been easy to prove the pernicious influence of serum treatment; consequently we believe that this possibility cannot be excluded in the use of antistreptococcal serum in the human subject. There can be no doubt that quite frequently mice were killed by both normal and antistreptococcal serum.

Any endeavour to determine the value of antistreptococcal serum from the results obtained in the human subject is unsatisfactory, for it is impossible to get similar untreated control cases.

The first series of cases with which we shall deal illustrates the variable effects of antistreptococcal therapeutic sera. In a large group of cases no really definite effect could be observed from the experimental use of these sera in the artificially infected mice, and this corresponds to a very common experience of the physician who uses antistreptococcal serum therapeutically in man. As illustrative of this group we may take the streptococcus derived from Case I. Of the emulsion 0·3 cubic centimetre injected intraperitoneally into the four mice caused the death of all the animals within twenty-four and a half hours, so that the strain was of high virulence, in terms of virulence of streptococcal strains as they are usually obtained direct from man. Half the animals receiving 0·03 cubic centimetre of the emulsion were dead in seven days, consequently the test dose of culture had ten 50% fatal doses at seven days in the amount given. The effects of normal horse serum and antistreptococcal sera C and CP were apparently negligible. One animal out of each group of four survived until the second day, otherwise all the animals died within the twenty-four hours. The details of the examination of this strain are set out in Table I.

Case VI illustrates the same point. The strain as isolated was fairly virulent. When administered

TABLE VI.

Case VI: Puerperal Septicæmia.

23/3/29. Blood culture taken.
25/3/29. Found positive—hæmolytic streptococcus.
Virulence and protection tests carried out on March 26, 1929, at 1 p.m.

No. of Mouse.	Dose Given.	Days of Observation. 1 27/3/29	2	3	4	5	6	7	8	9	10	11	12	Average Time of Death.
1	26/3/29 0·3 c.cm. Emulsion.	f.d. 9 a.m.												24 hours.
2		f.d. 9 a.m.												
3		f.d. 9 a.m.												
4		f.d. 9 a.m.												
5	26/3/29 0·03 c.cm. Emulsion.	–	–	–	–	–	–	–	–	–	–	+		
6		–	–	–	–	–	–	–	–	–	–	–	+	
7		–	–	–	–	–	–	–	–	–	–	–	–	
8		–	–	–	–	–	–	–	–	–	–	–	–	
9	26/3/29 0·3 c.cm. Heat-killed Emulsion.	–	–	–	–	–	–	–	–	–	–	–	–	Killed at the end of 6 weeks. *Post mortem*, N.A.D.
10		–	–	–	–	–	–	–	–	–	–	–	–	
11		–	–	–	–	–	–	–	–	–	–	–	–	
12		–	–	–	–	–	–	–	–	–	–	–	–	
13	26/3/29 0·3 c.cm. Emulsion + 0·2 c.cm. N.H.S.	f.d. 9 a.m.												24 hours.
14		f.d. 9 a.m.												
15		f.d. 9 a.m.												
16		f.d. 9 a.m.												
17	26/3/29 0·3 c.cm. Emulsion + 0·2 c.cm. Serum C.	f.d. 9 a.m.												24 hours.
18		f.d. 9 a.m.												
19		f.d. 9 a.m.												
20		f.d. 9 a.m.												
21	26/3/29 0·3 c.cm. Emulsion + 0·2 c.cm. Serum C.P.	f.d. 9 a.m.												24 hours.
22		f.d. 9 a.m.												
23		f.d. 9 a.m.												
24		f.d. 9 a.m.												
25	26/3/29 0·3 c.cm. Emulsion + 0·2 c.cm. Serum B.	f.d. 9 a.m.												24 hours.
26		f.d. 9 a.m.												
27		f.d. 9 a.m.												
28		f.d. 9 a.m.												
29	25/3/29 0·2 c.cm. N.H.S.	f.d. 9 a.m.												24 hours.
30		f.d. 9 a.m.												
31	26/3/29	f.d. 9 a.m.												
32	0·3 c.cm. Emulsion.	f.d. 9 a.m.												
33	25/3/29 0·2 c.cm. Serum C.	f.d. 9 a.m.												24 hours.
34		f.d. 9 a.m.												
35	26/3/29	f.d. 9 a.m.												
36	0·3 c.cm. Emulsion.	+11 a.m.												
37	25/3/29 0·2 c.cm. Serum C.P.	f.d. 9 a.m.												24 hours.
38		f.d. 9 a.m.												
39	26/3/29	f.d. 9 a.m.												
40	0·3 c.cm. Emulsion.	f.d. 9 a.m.												
41	25/3/29 0·2 c.cm. Serum B.	f.d. 9 a.m.												24 hours.
42		f.d. 9 a.m.												
43	26/3/29	f.d. 9 a.m.												
44	0·3 c.cm. Emulsion.	f.d. 9 a.m.												

with normal horse serum, antistreptococcal sera C, CP or B, no saving power was exercised by any of them.

The sera were also used prophylactically, that is to say, they were injected intraperitoneally into the mice the day preceding the injection of emulsion. Here again no evidence of saving power was shown. The test dose of emulsion used in this case was ten 50% fatal doses at twelve days. This experiment is of interest further in so far as killed bacteria were given to four mice as a control to see if the bacterial protein itself might be toxic. The emulsion was killed by exposure to a temperature of 80° C. for thirty minutes; from the table (number VI) it is seen that the bacterial protein so treated had not itself any recognizable degree of toxicity.

The streptococcus isolated from Case VII (*purpura hæmorrhagica*) had a high degree of virulence and infections with it were not affected favourably by any therapeutic serum. In this case the serum used prophylactically was given in 0·5 cubic centimetre quantities and was possibly valuable in one instance, when two animals survived out of the four, one for one month and one for two months, but these survivals may have been mere matters of chance, though we think this unlikely. Portion of this experiment was repeated about two years later (see Table VIIA). The strain had lost very

TABLE VII.

Case VII: Purpura Hæmorrhagica.

5/4/29. Blood culture taken.
6/4/29. Found Positive—hæmolytic streptococcus.
Virulence and protection tests carried out on April 9, 1929, at 1 p.m.

No. of Mouse.	Dose Given.	Days of Observation. 1 10/4/29	2	3	4	5	6	7	10	30	Remarks.	Time Taken for Half the Animals to Die.
1	9/4/29 0·3 c.cm. Emulsion.	f.d. 9 a.m.										1 day.
2		f.d. 9 a.m.										
3		f.d. 9 a.m.										
4		f.d. 9 a.m.										
5	9/4/29 0·03 c.cm. Emulsion.	f.d. 9 a.m.										6 days.
6		–	–	–	–	–	+					
7		–	–	–	–	–	–	–	–	–	Killed at end of 2 months *Post mortem*, N.A.D.	
8		–	–	–	–	–	–	–	–	–		
9	9/4/29 0·3 c.cm. Heat-killed Emulsion.	–	–	–	–	–	–	–	–	–	Killed at end of 2 months *Post mortem*, N.A.D.	
10		–	–	–	–	–	–	–	–	–		
11		–	–	–	–	–	–	–	–	–		
12		–	–	–	–	–	–	–	–	–		
13	9/4/29 0·3 c.cm. Emulsion + 0·2 c.cm. N.H.S.	f.d. 9 a.m.										1 day.
14		f.d. 9 a.m.										
15		f.d. 9 a.m.										
16		f.d. 9 a.m.										
17	9/4/29 0·3 c.cm. Emulsion + 0·2 c.cm. Serum C.	f.d. 9 a.m.										1 day.
18		f.d. 9 a.m.										
19		f.d. 9 a.m.										
20		f.d. 9 a.m.										
21	9/4/29 0·3 c.cm. Emulsion + 0·2 c.cm. Serum C.P.	f.d. 9 a.m.										1 day.
22		f.d. 9 a.m.										
23		+3 p.m.									Died on 24th day.	
24		–	–	–	–	–	–					
25	9/4/29 0·3 c.cm. Emulsion + 0·2 c.cm. Serum B.	f.d. 9 a.m.										1 day.
26		f.d. 9 a.m.										
27		f.d. 9 a.m.										
28		f.d. 9 a.m.										
29	8/4/29 0·5 c.cm. N.H.S.	f.d. 9 a.m.										1 day.
30		f.d. 9 a.m.										
31	9/4/29	f.d. 9 a.m.										
32	0·3 c.cm. Emulsion	f.d. 9 a.m.										
33	8/4/29 0·5 c.cm. Serum C.	f.d. 9 a.m.										1 day.
34		f.d. 9 a.m.										
35	9/4/29	f.d. 9 a.m.										
36	0·3 c.cm. Emulsion.	f.d. 9 a.m.										
37	8/4/29 0·5 c.cm. Serum C.P.	f.d. 9 a.m.										1 day.
38		+12 noon										
39	9/4/29	+12 noon									Died on 41st day.	
40	0·3 c.cm. Emulsion.	–	–	–	–	–	–	–	–			
41	8/4/29 0·5 c.cm. Serum B.	f.d. 9 a.m.										1 day.
42		f.d. 9 a.m.										
43	9/4/29	–	–	–	–	–	–	–	–	+		
44	0·3 c.cm. Emulsion.	–	–	–	–	–	–	–	–	–	Died at end of 2 months.	

little of its virulence and serum was again useless. The striking thing about these experimental infections is the uselessness of serum used therapeutically.

Cases XV and XX similarly illustrate the uselessness of antistreptococcal therapeutic sera in mice infected with strains of fairly high virulence coming direct from the human subject.

It is generally believed by the clinician that occasional cases are benefited by the use of antistreptococcal serum, and we have also occasionally found benefit to follow in the case of our artificially infected mice. For example, the streptococcus of Case V killed in an average time of two days in the test dose, but in the group treated simultaneously with antistreptococcal serum B, 5·5 days were required to kill. This experiment was repeated with the results set out in Table VA, where an almost exactly similar result is seen, the test dose killing in an average time of 2·5 days and antistreptococcal serum B enabling the animals to survive for six and a half days. The other sera had practically no effect or only a very slight effect.

The streptococcus of Case X killed in the standard dose in one day, whereas the animals treated with antistreptococcal serum CP survived 4·5 days.

The streptococcus of Case XIII shows yet more strikingly the value of serum treatment. Nine and

TABLE VIIA.

Case VII: Purpura Hæmorrhagica.

Virulence and protection tests carried out on July 31, 1931.

No. of Mouse.	Dose Given.	Days of Observation.			Remarks.
		1	2	3	
1	0·3 c.cm. Emulsion.	+			
2		+			
3		+			
4		+			
5	0·03 c.cm. Emulsion.	−	−	−	Killed at the end of 6 weeks. *Post mortem*, N.A.D.
6		−	−	−	
7		−	−	−	
8		−	−	−	
9	0·3 c.cm. Emulsion + 0·2 c.cm. N.H.S.	+			
10		+			
11		+			
12		−	+		
13	0·3 c.cm. Emulsion + 0·2 c.cm. Serum A.C.	+			
14		+			
15		+			
16		+			
17	0·3 c.cm. Emulsion + 0·2 c.cm. Serum C.	+			
18		+			
19		+			
20		−	−	−	Killed at end of 6 weeks. *Post mortem*, N.A.D.

three-quarter days was the average time of death with the standard dose of emulsion. With antistreptococcal serum CP one animal died on the thirty-ninth day, one on the hundred and thirty-first day, and, our patience being exhausted, two had to be killed on the hundred and forty-second day. The antistreptococcal serum C was even more effective, the first mouse dying after ninety-five days. The antistreptococcal serum B enabled half the animals to survive up to the fifty-seventh day, when they were destroyed. Antistreptococcal serum AU was also extremely effective, the second animal out of four dying in seventy-eight days and the third in ninety-four days. Normal horse serum, however, seemed also to have a very definitely protective influence.

In the animals that survived for long periods, abscesses in the neighbourhood of the liver were very commonly present. Occasionally streptococci were recovered from the heart's blood *post mortem*, suggesting that some of the animals had chronic septicæmia, but this was unusual. One gained the impression from a consideration of these animals that the serum treatment of infections with this strain was of immense value, and if it had been supplemented by adequate surgery, many of the animals would probably have recovered permanently.

While Case XIII shows that all sera were valuable, very different results were found in the case of other streptococci. The streptococcus of Case XIV is of interest in this regard. The average time of death after the standard dose of this streptococcus was fifteen and a quarter days. With normal horse serum it was 36·25 days, but with antistreptococcal serum C it was only 6·5 days, so that, while the normal horse serum was of definite value, the antistreptococcal serum C was just as definitely deleterious. This experiment was repeated on a small scale when it was found that the organism had lost a great deal of its virulence, forty-six days being required before half the animals receiving the test dose died. Nevertheless, in the case of the mice that received antistreptococcal serum C simultaneously, half the mice were dead in nine days, very definitely confirming the result that we had obtained in the first instance.

From Mouse 3 of the experiment of November 30, 1928 (see Table XIV), a streptococcus was recovered from the liver abscess and its virulence tested, when it was found to kill in an average time of 3·75 days as against the 15·25 days of the original streptococcus. If no contamination with a fresh streptococcus from the intestine or elsewhere had occurred, then there was a very definite increase of virulence from the single prolonged passage.

The streptococcus from Case XI is worthy of mention, for the large dose of organisms took longer to kill than the small dose, the single occasion on which this result was obtained. This may have been due to the small number of mice employed in the test.

In the streptococcus from Case XII a small degree of virulence only was found, 12·25 days being the average time of death with the standard dose. Out of five sera tested one only had a favourable influence on the experimental infection, the other sera having apparently very slight detrimental effects, but antistreptococcal serum AU prolonged the average duration of life after the test dose by more than 100%.

The streptococcus from Case IX was not favourably affected by any therapeutic serum, though antistreptococcal sera AU and B, used prophylactically in 0·5 cubic centimetre quantities, were of definite value.

We have already drawn attention in regard to the streptococcus from Case XIV to the possibly deleterious effect of serum treatment. We have found it so frequently that we consider it to be the main result of our work and a result of great importance to the clinician. As illustrative of this effect we shall take the streptococcus of Case XXI (see Table XXI). It was tested in the usual way and was found to be of relatively low virulence, five days being required to kill half the animals when using the standard dose of the emulsion. When this dose, however, was combined with normal horse serum or antistreptococcal serum of any of the three brands available, or with scarlet fever antitoxin, half the animals died within one or two days. If these deaths from the emulsion alone were in any way due to the streptococcal skin toxin, one would have imagined that the scarlet fever antitoxin at least would have delayed death. It had in fact only a strikingly detrimental influence. These results were so important that we determined to repeat part of the experiment with such a number of mice as would give reasonable certainty of the general result. The results of this experiment are shown in Table XXIA, from which we see again that half of the fourteen animals having the standard emulsion only died in five days, that nine-fourteenths of

TABLE VIII.

Case VIII: Subdeltoid Abscess.

5/4/29. Culture from pus.
6/4/29. Found positive—hæmolytic streptococcus.
Virulence and protection tests carried out on April 9, 1929, at 2 p.m.

No. of Mouse.	Dose Given.	Days of Observation.												Time Taken for Half the Animals to Die.
		1 10/4/29	2	3	4	5	6	7	8	9	10	13	30	
	9/4/29													
1	0·3 c.cm. Emulsion.	–	+											7 days.
2		–	–	–	–	–	–	+						
3		–	–	–	–	–	–	–	–	–	–	+		
4		–	–	–	–	–	–	–	–	–	–	–	+	
	9/4/29													
5	0·03 c.cm. Emulsion.	–	–	–	–	–	–	–	–	–	–	–	+	
6		–	–	–	–	–	–	–	–	–	–	–	–	
7		–	–	–	–	–	–	–	–	–	–	–	–	
8		–	–	–	–	–	–	–	–	–	–	–	–	
	9/4/29													
9	0·3 c.cm. Heat-killed	–	–	–	–	–	–	–	–	–	–	–	–	
10	Emulsion.	–	–	–	–	–	–	–	–	–	–	–	–	
11		–	–	–	–	–	–	–	–	–	–	–	–	
12		–	–	–	–	–	–	–	–	–	–	–	–	
	9/4/29													
13	0·3 c.cm. Emulsion.	–	–	+										
14	0·2 c.cm. N.H.S.	–	–	–	–	–	+							6 days.
15		–	–	–	–	–	–	–	–	–	–	+		
16		–	–	–	–	–	–	–	–	–	–	+		
	9/4/29													
17	0·3 c.cm. Emulsion +	–	–	–	–	–	+							
18	0·2 c.cm. Serum C.	–	–	–	–	–	+							6 days.
19		–	–	–	–	–	–	+						
20		–	–	–	–	–	–	–	–	–	–	–	–	
	9/4/29													
21	0·3 c.cm. Emulsion +	–	–	–	–	–	–	+						
22	0·2 c.cm. Serum C.P.	–	–	–	–	–	–	–	–	–	+			10 days.
23		–	–	–	–	–	–	–	–	–	–	+		
24		–	–	–	–	–	–	–	–	–	–	–	+	
	9/4/29													
25	0·3 c.cm. Emulsion +	–	–	–	–	–	–	+						
26	0·2 c.cm. Serum B.	–	–	–	–	–	–	–	–	–	–	+		13 days.
27		–	–	–	–	–	–	–	–	–	–	–	+	
28		–	–	–	–	–	–	–	–	–	–	–	–	
	8/4/29													
29	0·5 c.cm. N.H.S.	–	–	–	+									
30		–	–	–	–	+								5 days.
31	9/4/29	–	–	–	–	–	+							
32	0·3 c.cm. Emulsion.	–	–	–	–	–	–	+						
	8/4/29													
33	0·5 c.cm. Serum C.	–	–	–	–	–	–	+						
34		–	–	–	–	–	–	–	–	–	–	+		13 days.
35	9/4/29	–	–	–	–	–	–	–	–	–	–	–	+	
36	0·3 c.cm. Emulsion.	–	–	–	–	–	–	–	–	–	–	–	–	
	8/4/29													
37	0·5 c.cm. Serum C.P.	–	–	–	–	–	+							
38		–	–	–	–	–	–	+						7 days.
39	9/4/29	–	–	–	–	–	–	–	–	–	–	+		
40	0·3 c.cm. Emulsion.	–	–	–	–	–	–	–	–	–	–	–	+	
	8/4/29													
41	0·5 c.cm. Serum B.	–	–	+										
42		–	–	–	–	–	–	+						7 days.
43	9/4/29	–	–	–	–	–	–	–	–	–	–	–	–	
44	0·3 c.cm. Emulsion.	–	–	–	–	–	–	–	–	–	–	–	–	

the total number of animals that received normal serum with the bacteria died in one day, and eleven-fourteenths of those receiving antistreptococcal serum simultaneously with the bacteria, so that both the normal and antistreptococcal sera were highly deleterious, especially the antistreptococcal. This deleterious effect is also shown by the fact that five out of the fourteen animals receiving the test dose of bacteria only survived six weeks, two only of the fourteen receiving treatment with normal serum, and not one of those receiving treatment with specific serum. A group of fourteen animals was used as a control of the environment, from which it is seen that the mice were kept in such a way as to give reasonable assurance of the correctness of the general result. One mouse died from pneumonia on the third day, but, apart from that, all the other thirteen control animals survived for the six weeks, and on *post mortem* examinations being made, showed no significant abnormalities.

The streptococcus from Case XXIII, also of low virulence, the standard dose taking ten days to kill half the animals inoculated, was rendered highly virulent by simultaneous treatment of the animals with any one of the six sera dealt with.

The same pernicious influence of serum treatment is seen in Table XXII. It is also slightly evidenced in the experiment recorded in Table XVIII.

Avirulent Strain.—In the case of the streptococcus isolated from Case II, the standard dose was

TABLE IX.

Case IX: Chorea for Three Weeks; Suppurating Ingrowing Toenail for Years.

5/4/29. Pus from toe cultured.
6/4/29. Found positive—hæmolytic streptococcus.
Virulence and protection tests carried out on April 11, 1929, at 12 noon.

No. of Mouse.	Dose Given.	Days of Observation.													Time Taken for Half the Animals to Die.
		1 12/4/29	2	3	4	5	6	7	8	9	10	14	15	19	
	11/4/29														
1	0·3 c.cm. Emulsion.	−	−	−	+										4 days.
2		−	−	−	+										
3		−	−	−	+										
4		−	−	−	−	−	−	−	−	−	−	−	−	−	
	11/4/29														
5	0·03 c.cm. Emulsion.	−	−	−	−	−	−	−	−	−	−	+			19 days.
6		−	−	−	−	−	−	−	−	−	−	−	−	+	
7		−	−	−	−	−	−	−	−	−	−	−	−	−	
8		−	−	−	−	−	−	−	−	−	−	−	−	−	
	11/4/29														
9	0·3 c.cm. Heat-killed	−	−	−	−	−	−	−	−	−	−	−	−	−	
10	Emulsion.	−	−	−	−	−	−	−	−	−	−	−	−	−	
11		−	−	−	−	−	−	−	−	−	−	−	−	−	
12		−	−	−	−	−	−	−	−	−	−	−	−	−	
	11/4/29														
13	0·3 c.cm. Emulsion +	+3 p.m.													
14	0·2 c.cm. N.H.S.	−	+												2 days.
15		−	−	+											
16		−	−	−	−	−	−	−	−	−	−	+			
	11/4/29														
17	0·3 c.cm. Emulsion +	+3 p.m.													
18	0·2 c.cm. Serum C.	−	−	+											3 days.
19		−	−	+											
20		−	−	−	−	−	−	−	−	−	−	+			
	11/4/29														
21	0·3 c.cm. Emulsion +	+3 p.m.													
22	0·2 c.cm. Serum C.P.	−	+												2 days.
23		−	−	−	−	+									
24		−	−	−	−	+									
	11/4/29														
25	0·3 c.cm. Emulsion +	f.d. 9 a.m.													
26	0·2 c.cm. Serum B.	+3 p.m.													1 day.
27		−	−	−	−	−	−	−	−	−	−	−	−	+	
28		−	−	−	−	−	−	−	−	−	−	−	−	+	
	11/4/29														
29	0·3 c.cm. Emulsion +	+3 p.m.													
30	0·2 c.cm. Serum A.U.	+4 p.m.													1 day.
31		−	+												
32		−	−	−	−	−	−	−	−	−	−	+			
	10/4/29														
33	0·5 c.cm. N.H.S.	+4 p.m.													
34		+5 p.m.													1 day.
35	11/4/29	−	+												
36	0·3 c.cm. Emulsion.	−	+												
	10/4/29														
37	0·5 c.cm. Serum C.	−	+												
38		−	−	+											3 days.
39	11/4/29	−	−	−	+										
40	0·3 c.cm. Emulsion.	−	−	−	−	−	−	−	−	−	−	−	−	−	
	10/4/29														
41	0·5 c.cm. Serum C.P.	−	−	−	+										
42		−	−	−	−	+									5 days.
43	11/4/29	−	−	−	−	−	+								
44	0·3 c.cm. Emulsion.	−	−	−	−	−	−	−	−	−					
	10/4/29														
45	0·5 c.cm. Serum B.	−	−	−	+										
46		−	−	−	−	−	−	−	−	−	−	−	+		15 days.
47	11/4/29	−	−	−	−	−	−	−	−	−	−	−	−	−	
48	0·3 c.cm. Emulsion.	−	−	−	−	−	−	−	−	−	−	−	−	−	
	10/4/29														
49	0·5 c.cm. Serum A.U.	−	−	−	−	−	−	−	−	−	+				
50		−	−	−	−	−	−	−	−	−	−	−	+		15 days.
51	11/4/29	−	−	−	−	−	−	−	−	−	−	−	−	+	
52	0·3 c.cm. Emulsion.	−	−	−	−	−	−	−	−	−	−	−	−	−	

unable to kill either of the animals and the addition of serum did not make the dose fatal.

When the 50% death time was dealt with, the streptococcus from Case VIII was seen to be of small virulence, and though two sera seemed to be of slight value, one in treatment and one in prophylaxis, the two sera were not the same in the two cases. It would be difficult to say how much of this result represents real truth, for, when the average time of death is taken, the results are somewhat different. In the experiments on prophylaxis, 0·5 cubic centimetre was the quantity of serum used. Unfortunately, we did not repeat the experiment.

The infections with the streptococcus from Case III do not show any very significant effects of serum treatment.

TABLE X.

Case X: Septicæmia.

13/8/28. Blood culture taken.
14/8/28. Found positive—hæmolytic streptococcus.
Virulence and protection tests carried out on August 15, 1928, at 4 p.m.

No. of Mouse.	Dose Given.	Days of Observation. 1 16/8/28	2	3	4	5	6	7	8	9	10	Average Time of Death.
1	0·03 c.cm. Emulsion.	–	+									
2		–	–	–	–	–	–	–	–	–	–	
3	0·3 c.cm. Emulsion.	+f.d. 4 p.m.										1 day.
4		+f.d. 5 p.m.										
5	0·3 c.cm. Emulsion +	+f.d. 4.30 p.m.										1 day.
6	0·2 c.cm. N.H.S.	+f.d. 5.30 p.m.										
7	0·3 c.cm. Emulsion +	–	+									3 days.
8	0·2 c.cm. Serum C.	–	–	–	+							
9	0·3 c.cm. Emulsion +	–	+									4·5 days.
10	0·2 c.cm. Serum C.P.	–	–	–	–	–	–	+				

TABLE XI.

Case XI: Osteomyelitis of Thigh.

5/10/28. Pus cultured.
Found positive—hæmolytic streptococcus.
Virulence and protection tests carried out on October 8, 1928, at 4 p.m.

No. of Mouse.	Dose Given.	Days of Observation. 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	23	30	Average Time of Death.
1	0·03 c.cm. Emulsion.	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	+			15 days.
2		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–				
3	0·3 c.cm. Emulsion.	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	+		19 days.
4]		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–				
5	0·3 c.cm. Emulsion +	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	+				13·5 days.
6]	0·2 c.cm. N.H.S.	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–					
7]	0·3 c.cm. Emulsion +	–	–	–	–	–	–	–	–	+											9 days.
8]	0·2 c.cm. Serum C.	–	–	–	–	–	–	–	–	+											
9	0·3 c.cm. Emulsion +	–	–	–	–	–	–	–	+												19 days.
10	0·2 c.cm. Serum C.P.	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	

TABLE XII.

Case XII: Wound—After Removal of Breast.

24/11/28. Pus cultured.
Found positive—hæmolytic streptococcus.
Virulence and protection tests carried out on November 27, 1928, at 6 p.m.

No. of Mouse.	Dose Given.	Days of Observation. 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	20	26	55	Average Time of Death.
1	0·03 c.cm. Emulsion.	–	–	–	+															
2		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–				
3		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–				
4		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–				
5	0·3 c.cm. Emulsion.	–	–	–	–	–	–	–	+											12·25 days.
6		–	–	–	–	–	–	–	–	+										
7		–	–	–	–	–	–	–	–	–	–	–	+							
8		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+			
9	0·3 c.cm. Emulsion +	–	–	+																8·0 days.
10	0·2 c.cm. N.H.S.	–	–	–	–	–	–	+												
11		–	–	–	–	–	–	–	–	–	–	+								
12		–	–	–	–	–	–	–	–	–	–	+								
13	0·3 c.cm. Emulsion +	–	–	–	–	–	–	+												8·5 days.
14	0·2 c.cm. Serum C.P.	–	–	–	–	–	–	+												
15		–	–	–	–	–	–	–	+											
16		–	–	–	–	–	–	–	–	–	–	–	+							
17	0·3 c.cm. Emulsion +	–	–	–	–	–	–	+												10·25 days.
18	0·2 c.cm. Serum C.	–	–	–	–	–	–	–	–	–	–	+								
19		–	–	–	–	–	–	–	–	–	–	+								
20		–	–	–	–	–	–	–	–	–	–	–	+							
21	0·3 c.cm. Emulsion +	–	+																	8·25 days.
22	0·2 c.cm. Serum B.	–	–	–	–	+														
23		–	–	–	–	–	–	–	–	–	–	+								
24		–	–	–	–	–	–	–	–	–	–	–	–	–	–	+				
25	0·3 c.cm. Emulsion +	–	–	–	–	+														26·5 days.
26	0·2 c.cm. Serum A.U.	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+			
27		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+		
28		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	

TABLE XIII.

Case XIII: Suppurative Arthritis.

25/11/28. Fluid from knee joint cultured.
26/11/28. Found positive—hæmolytic streptococcus.
Virulence and protection tests carried out on November 27, 1928, at 7 p.m.

No. of Mouse.	Dose Given.	Days of Observation. 1	2	3	4	5	6	7	8	9	10	11	12	13	27	39	49	55	57	78	94	95	131	142	*Post Mortem* Result.
1	0·03 c.cm. Emulsion.	–	–	–	+																				
2		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+K								N.A.D. No streptococci recovered in cultures of heart's blood.
3		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+K								
4		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+K								
5	0·3 c.cm. Emulsion	–	–	–	–	+												Average time of death: 9·75 days.							
6		–	–	–	–	–	–	–	–	+															
7		–	–	–	–	–	–	–	–	–	–	–	+												
8		–	–	–	–	–	–	–	–	–	–	–	–	+											
9	0·3 c.cm. Emulsion +	–	–	–	+																				
10	0·2 c.cm. N.H.S.	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+K							Liver abscess, crowded with streptococci. Hæmolytic streptococci recovered from heart blood.
11		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+K							Liver abscess, streptococci recovered. Heart blood normal.
12		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+K							Liver abscess, streptococci recovered. Heart blood normal.
13	0·3 c.cm. Emulsion +	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+									
14	0·2 c.cm. Serum C.P.	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+		N.A.D. Heart blood normal.
15		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+K	
16		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+K	
17	0·3 c.cm. Emulsion +	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+			
18	0·2 c.cm. Serum C.	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+K	N.A.D. Heart blood normal.
19		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+K	
20		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+K	
21	0·3 c.cm. Emulsion +	–	–	–	–	–	–	–	–	–	–	–	–	–	+										
22	0·2 c.cm. Serum B.	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+									
23		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+K						N.A.D. Heart blood normal.
24		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+K						
25	0·3 c.cm. Emulsion	–	–	–	–	–	–	+																	
26	0·2 c.cm. Serum A.U.	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+					N.A.D. Heart blood normal.
27		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+				Plastic peritonitis. Large liver abscess. Hæmolytic streptococci recovered from heart blood.
28		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+K	N.A.D.

Controls.

These results require careful controls, which we might now discuss. The general plan of the experiments is that followed in the testing of pneumococcal serum. The amount of serum given is the amount usually used in pneumococcal serum testing. The number of fatal doses of the bacterial emulsion is very much less than that used in pneumococcal work, and the total number of bacteria injected is substantially more. These two slight departures from the technique of pneumococcal work were inevitable because of the low degree of virulence of the strains that we isolated direct from man. The mixing of bacteria with a serum containing antiseptic might be held to give an opportunity for the antiseptic to disturb the results. We cannot accept this possibility, for in the majority of cases the sera with their contained antiseptic had no substantial effect on the experimental infection. Secondly (Table XXV), recounting the testing of the value of Type I pneumococcal serum in the treatment of the experimental infections of mice by strain "Martin", a virulent Type I pneumococcus direct from the human subject, shows that the amount of antiseptic present was not sufficient to injure the defensive mechanism of the animal, since all the four animals treated with the specific serum survived for the period of six weeks in spite of the contained antiseptic. Further, the four animals that were treated with normal horse serum died at the same time as those receiving the emulsion without it. If the antiseptic of the normal horse serum had had an inhibitory or deleterious effect on the organisms, then one would have expected the time of death to be delayed. The different manufacturers used different antiseptics, but the good, indifferent and evil effects resulted equally from the products of each manufacturer. From these various considerations, therefore, we believe the antiseptic contained in the serum played no significant part in our results.

The Keeping of Mice.

On more than one occasion it has been our experience, when sending a group of mice to another laboratory, to have a complaint to the effect that perhaps 15% to 20% of the animals had died soon after arrival at the new laboratory, and this has been put down to the bad health of the mice. We have found, however, that it has been invariably due to an unsuitable environment. Mice cannot stand any great exposure to cold, but if they are kept in a well warmed room and properly tended, the mortality is not such as to affect our experimental results. We have environmental control mice perpetually in the same room where the experimental mice are kept. These control mice are dis-

TABLE XIV.

Case XIV: Cellulitis of the Arm.

13/11/28. Pus cultured.
14/11/28. Found positive—hæmolytic streptococcus.
Virulence and protection tests carried out on November 17, 1928, at 12 noon.

No. of Mouse.	Dose Given.	Days of Observation. 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	23	24	49	87	Average Time of Death.	*Post Mortem* Results.
1	0·03 c.cm. Emulsion.	–	–	–	–	–	–	+																		
2		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+K		N.A.D. Heart blood culture no growth.
3		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+K		
4		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+K		
5	0·3 c.cm. Emulsion.	–	–	–	–	–	–	–	–	–	–	+														
6		–	–	–	–	–	–	–	–	–	–	–	+												15·25 days.	
7		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+								
8		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+						
9	0·3 c.cm. Emulsion.	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+					
10	0·2 c.cm. N.H.S.	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+			36·25 days.	
11		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+			
12		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+			
13	0·3 c.cm. Emulsion +	–	–	–	–	–	+																			
14	0·2 c.cm. Serum C.	–	–	–	–	–	+																		6·5 days	
15		–	–	–	–	–	–	+																		
16		–	–	–	–	–	–	+																		
17	0·3 c.cm. Emulsion +	–	–	–	–	–	–	–	–	–	+															
18	0·2 c.cm. Serum C.P.	–	–	–	–	–	–	–	–	–	–	+													12·75 days.	
19		–	–	–	–	–	–	–	–	–	–	–	+													
20		–	–	–	–	–	–	–	–	–	–	–	–	–	+											

Experiment Repeated on November 30, 1928.

No.	Dose Given.	Days of Observation. 1	2	3	4	5	6	7	8	9	10	20	46	52	*Post Mortem* Results.
1	0·3 c.cm. Emulsion.	–	–	–	–	–	–	–	–	–	+				
2		–	–	–	–	–	–	–	–	–	–	–	+		
3		–	–	–	–	–	–	–	–	–	–	–	–	+K	Both mice apparently healthy when killed. Each had liver abscess. Hæmolytic streptococci recovered from each.
4		–	–	–	–	–	–	–	–	–	–	–	–	+K	
5	0·3 c.cm. Emulsion +	–	–	–	+										
6	0·2 c.cm. Serum C.	–	–	–	–	–	–	–	–	+					
7		–	–	–	–	–	–	–	–	–	–	+			
8		–	–	–	–	–	–	–	–	–	–	–	–	+K	Apparently healthy when killed, except for small lump on left side. On *post mortem* examination lump adherent to stomach. Had pushed through belly wall and was adherent to skin. Abscess full of pus, and hæmolytic streptococci recovered.

Hæmolytic streptococcus recovered from liver abscess. Experiment carried out on November 30, 1928. Mouse Number 3. January 25, 1929.

No.	Dose Given.	Days of Observation. 1	2	3	4	5	6	7	8	9	10	11	12	13	87	Average Time of Death.	*Post Mortem* Results.
1	0·03 c.cm. Emulsion.	–	–	–	–	+											
2		–	–	–	–	–	–	–	–	+							
3		–	–	–	–	–	–	–	–	–	–	–	+				N.A.D macroscopically. Hæmolytic streptococci recovered from heart blood.
4		–	–	–	–	–	–	–	–	–	–	–	–	–	+K		
5	0·3 c.cm. Emulsion.	–	+														
6		–	–	+												3·75 days.	
7		–	–	+													
8		–	–	–	–	–	–	–	–	–	–	–	–	+			N.A.D. macroscopically. Hæmolytic streptococci recovered from heart blood.

tributed in shallow earthenware jars in groups of four, and they are fed and tended exactly as the experimental animals. If the total number of controls is not divisible by four, then one jar contains a smaller number than four. In the case of fifty-eight control animals kept for six weeks in the experimental mouse room, three deaths occurred during the period. In no case did two deaths occur in one earthenware container. We therefore believe that though a small error may creep in in this way, it is not significant. These controls have been present at every season of the year, so that possibly deleterious effects of climatic change have been rigidly excluded.

TABLE XV.

Case XV: Scarlet Fever.

13/10/31. Hæmolytic streptococcus isolated from throat.
Virulence and protection tests carried out on October 16, 1931.

No. of Mouse.	Dose Given.	Days of Observation. 1	2	7	12	21	Remarks.
1	0·3 c.cm. Emulsion.	+					
2		+					
3		+					
4		+					
5	0·03 c.cm. Emulsion.	−	−	+			
6		−	−	−	+		
7		−	−	−	−	+	
8		−	−	−	−	−	Killed at end of 6 weeks. *Post mortem*, N.A.D.
9	0·3 c.cm. Emulsion +	+					
10	0·2 c.cm. N.H.S.	+					
11		+					
12		−	+				
13	0·3 c.cm. Emulsion +	+					
14	0·2 c.cm. Serum A.A.	+					
15		+					
16		+					

The Technique of Inoculation.

The technique of intraperitoneal inoculation is not entirely free from risk. To get a measure of the outside value of the risk, eighty animals have been inoculated with the serum alone, so that these animals provided a control of the environment, of the risk of puncturing the peritoneum and of the administration of the serum with its contained anti-

TABLE XVI.

Case XVI: Suppurative Prepatellar Bursitis.

2/7/31. Hæmolytic streptococcus isolated from fluid from knee.
Virulence and protection tests carried out on July 31, 1931.

No. of Mouse.	Dose Given.	Days of Observation. 1	2	4	5	8	9	11	13	15	20	Remarks.
1	0·3 c.cm. Emulsion.	−	+									
2		−	−	−	−	−	−	−	+			
3		−	−	−	−	−	−	−	−	−	−	Killed at end of 6 weeks.
4		−	−	−	−	−	−	−	−	−	−	*Post mortem*, N.A.D.
5	0·03 c.cm. Emulsion.	−	−	+								
6		−	−	−	−	−	−	−	−	−	−	Killed at end
7		−	−	−	−	−	−	−	−	−	−	of 6 weeks.
8		−	−	−	−	−	−	−	−	−	−	*Post mortem*, N.A.D.
9	0·3 c.cm. Emulsion +	−	−	−	+							
10	0·2 c.cm. N.H.S.	−	−	−	−	−	+					
11		−	−	−	−	−	+					
12		−	−	−	−	−	−	−	−	−	−	Killed at end of 6 weeks. *Post mortem*, N.A.D.
13	0·3 c.cm. Emulsion +	−	−	−	−	+						
14	0·2 c.cm. Serum A.C.	−	−	−	−	−	−	−	−	−	+	
15		−	−	−	−	−	−	−	−	−	−	Killed at end of 6 weeks. *Post mortem*, N.A.D
16		−	−	−	−	−	−	−	−	−	−	Killed at end of 6 weeks. *Post mortem*, liver abscess (streptococci).
17	0·3 c.cm. Emulsion +	−	−	−	−	−	+					
18	0·2 c.cm. Serum C.	−	−	−	−	−	−	+				
19		−	−	−	−	−	−	−	−	+		
20		−	−	−	−	−	−	−	−	−	+	

TABLE XVII.

Case XVII: Injury to Leg.

3/7/31. Hæmolytic streptococcus isolated.
Virulence and protection tests carried out on July 21, 1931

No. of Mouse.	Dose Given.	Days of Observation. 1	2	3	8	Remarks.
1	0·3 c.cm. Emulsion.	+				
2		−	+			
3		−	+			
4		−	−	−	+	
5	0·03 c.cm. Emulsion.	−	+			
6		−	−	−	−	Killed at the end of 6 weeks. *Post mortem*, N.A.D.
7		−	−	−	−	
8		−	−	−	−	
9	0·3 c.cm. Emulsion +	+				
10	0·2 c.cm. N.H.S.	−	+			
11		−	+			
12		−	−	+		
13	0·3 c.cm. Emulsion +	+				
14	0·2 c.cm. Serum A.C.	+				
15		−	+			
16		−	−	+		
17	0·3 c.cm. Emulsion +	+				
18	0·2 c.cm. Serum C.	+				
19		−	+			
20		−	+			

septic. Ten animals in the series have died within the six weeks; four animals only died in the first fortnight. There is, therefore, only a one in twenty risk of error in the case of any particular animal from this cause in the first fourteen days of our experiment, which is increased to one in eight after the lapse of six weeks. Having groups of four animals, we hold that these errors do not invalidate our general results. On several occasions killed organisms have been introduced into groups of animals in standard doses, sometimes with serum in addition, but in none of these cases has death ensued within the period of six weeks.

TABLE XVIII.

Case XVIII: Pustule on Leg.

11/7/31. Hæmolytic streptococcus isolated.
Virulence and protection tests carried out on July 21, 1931.

No. of Mouse.	Dose Given.	Days of Observation. 1	2	3	4	5	6	7	8	Remarks.
1	0·3 c.cm. Emulsion.	−	+							
2		−	−	−	+					
3		−	−	−	+					
4		−	−	−	−	−	−	+		
5	0·03 c.cm. Emulsion.	−	−	−	−	−	−	−	−	Killed after 6 weeks. *Post mortem*, liver abscess with streptococci.
6		−	−	−	−	−	−	−	−	Killed at end of 6 weeks. *Post mortem*, N.A.D.
7		−	−	−	−	−	−	−	−	
8		−	−	−	−	−	−	−	−	
9	0·3 c.cm. Emulsion +	+								
10	0·2 c.cm. N.H.S.	+								
11		−	+							
12		−	−	−	−	+				
13	0·3 c.cm. Emulsion +	+								
14	0·2 c.cm. Serum A.C.	−	−	+						
15		−	−	−	+					
16		−	−	−	−	−	+			
17	0·3 c.cm. Emulsion +	+								
18	0·2 c.cm. Serum C.	−	+							
19		−	+							
20		−	+							

Emulsion = 24 hour broth culture 2,000M/c.cm.

TABLE XIX.

Case XIX: Cellulitis of Arm.

15/7/31. Hæmolytic streptococcus isolated.
Virulence and protection tests carried out on July 21, 1931.

No. of Mouse.	Dose Given.	Days of Observation. 1	2	3	Remarks.
1	0·3 c.cm. Emulsion.	−	+		
2		−	+		
3		−	−	−	Killed at the end of 6 weeks.
4		−	−	−	*Post mortem*, N.A.D.
5	0·03 c.cm. Emulsion.	−	−	−	Killed at the end of 6 weeks.
6		−	−	−	*Post mortem*, N.A.D.
7		−	−	−	
8		−	−	−	
9	0·3 c.cm. Emulsion +	+			
10	0·2 c.cm. N.H.S.	−	+		
11		−	−	−	Killed at the end of 6 weeks.
12		−	−	−	*Post mortem*, N.A.D.
13	0·3 c.cm. Emulsion +	+			
14	0·2 c.cm. Serum A.C.	+			
15		+			Killed at the end of 6 weeks.
16		−	−	−	*Post mortem*, N.A.D.
17	0·3 c.cm. Emulsion +	+			
18	0·2 c.cm. Serum C.	−	+		
19		−	+		
20		−	+		

The Marking of Mice.

The marking of mice with carbol fuchsin has been avoided. If large marks are made with this dye there is a liability of carbolic poisoning, and when it is intended to keep the animals under observation for six weeks, inexperienced workers are liable to make dangerously large marks. Marking with dye solutions has, therefore, been avoided altogether.

Interpretation of Results.

In the light of these controls we have endeavoured to interpret our results.

TABLE XX.

Case XX: Septicæmia.

26/8/31. Hæmolytic streptococcus isolated from blood.
Virulence and protection tests carried out on October 6, 1931.

No. of Mouse.	Dose Given.	Days of Observation. 1	2	8	Remarks.
1	0·3 c.cm. Emulsion.	+			
2		+			
3		+			
4		+			
5	0·03 c.cm. Emulsion.	−	−	+	
6		−	−	−	Killed at end of 6 weeks.
7		−	−	−	*Post mortem*, N.A.D.
8		−	−	−	
9	0·3 c.cm. Emulsion +	+			
10	0·2 c.cm. N.H.S.	+			
11		+			
12		+			
13	0·3 c.cm. Emulsion +	+			
14	0·2 c.cm. Serum A.U.	+			
15		+			
16		+			
17	0·3 c.cm. Emulsion +	+			
18	0·2 c.cm. Serum C.	+			
19		+			
20		+			
21	0·3 c.cm. Emulsion +	+			
22	0·2 c.cm. Serum A.A.	+			
23		+			
24		+			

TABLE XXI.

Case XXI: Septic Abortion.

3/9/31. Hæmolytic streptococcus isolated from blood.
Virulence and protection tests carried out on September 8, 1931.

No. of Mouse.	Dose Given.	Days of Observation. 1	2	3	5	7	9	30	Remarks.
1	0·3 c.cm. Emulsion.	+							
2		−	−	−	+				
3		−	−	−	−	−	+		
4		−	−	−	−	−	−	+	
5	0·03 c.cm. Emulsion.	−	−	−	−	−	−	−	Killed at the end of 6 weeks.
6		−	−	−	−	−	−	−	*Post mortem*, N.A.D.
7		−	−	−	−	−	−	−	
8		−	−	−	−	−	−	−	
9	0·3 c.cm. Emulsion +	+							
10	0·2 c.cm. N.H.S.	−	+						
11		−	+						
12		−	−	−	−	−	−	−	Killed at end of 6 weeks. *Post mortem*, N.A.D.
13	0·3 c.cm. Emulsion +	+							
14	0·2 c.cm. Serum A.C.	+							
15		+							
16		+							
17	0·3 c.cm. Emulsion +	+							
18	0·2 c.cm. Serum C.	+							
19		+							
20		+							
21	0·3 c.cm. Emulsion +	+							
22	0·2 c.cm. Serum A.U.	+							
23		−	−	+					
24		−	−	−	−	+			
25	0·3 c.cm. Emulsion +	+							
26	0·2 c.cm. Serum A.A.	+							
27		+							
28		+							

Our first conclusion is that there is an element of danger in the use of therapeutic streptococcal serum which has not received recognition, and as far as our experiments in mice go, they suggest that it would be advisable to avoid the therapeutic use of this serum. When we come to consider why antistreptococcal serum should so frequently have disastrous results, we have to confess that we are not in a position to give any satisfactory answer. It has been shown by Dean[9] that the binding of complement and the precipitation tests occur most effectively in certain definite optimal proportions, and it may be that our erratic streptococcal results in mice will find some similar explanation of a quantitative character, but we ourselves have not had time to investigate this problem. Further, the Neisser-Wechsberg[10] phenomenon seems possibly to be an *in vitro* expression of the requirement of certain optimal proportions for effective bactericidal action.

Certain serum makers have described hypersensitiveness as occurring in horses undergoing streptococcal immunization, and it has occurred to us that we may possibly be transmitting passively this hypersensitive state to the treated mouse and so occasioning its early death.

One striking feature of our results is the close similarity between the effects of normal and antistreptococcal sera. They are not invariably similar, but quite frequently they are. This has suggested that either the antistreptococcal serum has, as a rule, only a very trifling antistreptococcal character or that normal horse serum must have some anti-

TABLE XXIA.

Case XXI: Septic Abortion.

3/9/31. Hæmolytic streptococcus isolated from blood.
Virulence and protection tests carried out on September 18, 1931.

No. of Mouse.	Dose Given.	Days of Observation. 1	2	3	5	6	7	9	33	38	Remarks.
29	0·3 c.cm. Emulsion.	+									
30		+									
31		−	+								
32		−	+								
33		−	−	−	+						
34		−	−	−	+						
35		−	−	−	+						
36		−	−	−	−	−	−	−	+		
37		−	−	−	−	−	−	−	−	+	
38		−	−	−	−	−	−	−	−	−	Killed at the end of 6 weeks. *Post mortem*, N.A.D.
39		−	−	−	−	−	−	−	−	−	
40		−	−	−	−	−	−	−	−	−	
41		−	−	−	−	−	−	−	−	−	
42		−	−	−	−	−	−	−	−	−	
43	0·3 c.cm. Emulsion + 0·2 c.cm. N.H.S.	+									
44		+									
45		+									
46		+									
47		+									
48		+									
49		+									
50		+									
51		+									
52		−	+								
53		−	−	−	−	−	+				
54		−	−	−	−	−	−	+			
55		−	−	−	−	−	−	−	−	−	Killed at end of 6 weeks. *Post mortem*, rib abscess (streptococci).
56		−	−	−	−	−	−	−	−	−	Killed at end of 6 weeks. *Post mortem*, N.A.D.
57	0·3 c.cm. Emulsion + 0·2 c.cm. Serum A.C.	+									
58		+									
59		+									
60		+									
61		+									
62		+									
63		+									
64		+									
65		+									
66		+									
67		+									
68		−	+								
69		−	+								
70		−	−	−	−	+					
71	Control.	−	−	+							Pneumonia.
72		−	−	−	−	−	−	−	−	−	
73		−	−	−	−	−	−	−	−	−	
74		−	−	−	−	−	−	−	−	−	
75		−	−	−	−	−	−	−	−	−	
76		−	−	−	−	−	−	−	−	−	Killed at end of 6 weeks. *Post mortem*, N.A.D.
77		−	−	−	−	−	−	−	−	−	
78		−	−	−	−	−	−	−	−	−	
79		−	−	−	−	−	−	−	−	−	
80		−	−	−	−	−	−	−	−	−	
81		−	−	−	−	−	−	−	−	−	
82		−	−	−	−	−	−	−	−	−	
83		−	−	−	−	−	−	−	−	−	
84		−	−	−	−	−	−	−	−	−	

streptococcal features, possibly from previously occurring natural infections in the horses from which the sera have been derived. To test this last possibility, Dr. Morgan, Director of the Commonwealth Serum Laboratories, was good enough to supply us with six normal sera from new horses which had never received any inoculation treatment. We added to these sera 0·3% of tricresol and tested their effect against experimental infections in the mouse.

The results are recorded in Table XXVI, from which we see that there are probably wide differences in the effects of normal sera on these experimental streptococcal infections.

TABLE XXII.

Case XXII: Possible Scarlet Fever Carrier.

15 9/31. Hæmolytic streptococcus isolated from nose.
Virulence and protection tests carried out on September 22, 1931.

No. of Mouse.	Dose Given.	Days of Observation. 1	2	3	6	12	18	30	Remarks.
1	0·3 c.cm. Emulsion.	+							
2		−	−	−	+				
3		−	−	−	−	+			
4		−	−	−	−	−	+		
5	0·03 c.cm. Emulsion.	−	−	−	−	−	−	+	*Post mortem*, liver abscess.
6		−	−	−	−	−	−	−	Killed at end of 6 weeks.
7		−	−	−	−	−	−	−	
8		−	−	−	−	−	−	−	*Post mortem*, N.A.D.
9	0·3 c.cm. Emulsion + 0·2 c.cm. N.H.S.	+							
10		+							
11		−	+						
12		−	−	+					
13	0·3 c.cm. Emulsion + 0·2 c.cm. Serum C.	+							
14		+							
15		−	+						
16		−	+						
17	0·3 c.cm. Emulsion + 0·2 c.cm. Serum A.U.	+							
18		+							
19		+							
20		−	+						
21	0·3 c.cm. Emulsion + 0·2 c.cm. Serum A.A.	+							
22		+							
23		+							
24		+							

TABLE XXIII.

Case XXIII: Lobar Pneumonia.

16/5/29 Hæmolytic streptococcus isolated from pus from pleural cavity.
Virulence and protection tests carried out on May 17, 1929.

No. of Mouse.	Dose Given.	Days of Observation. 1	2	3	6	10	11	18	Remarks.
1	0·3 c.cm. Emulsion.	−	−	+					
2		−	−	−	−	+			
3		−	−	−	−	−	+		
4		−	−	−	−	−	−	−	Killed at end of 6 weeks. *Post mortem*, N.A.D.
5	0·03 c.cm. Emulsion.	−	−	−	+				
6		−	−	−	−	−	−	+	
7		−	−	−	−	−	−	+	
8		−	−	−	−	−	−	−	Killed at end of 6 weeks. *Post mortem*, N.A.D.
9	0·3 c.cm. heat-killed Emulsion.	−	−	−	−	−	−	−	Killed at end of 6 weeks.
10		−	−	−	−	−	−	−	
11		−	−	−	−	−	−	−	
12		−	−	−	−	−	−	−	*Post mortem*, N.A.D.
13	0·3 c.cm. Emulsion + 0·2 c.cm. N.H.S.	+							
14		+							
15		+							
16		−	+						
17	0·3 c.cm. Emulsion + 0·2 c.cm. Serum C.	+							
18		+							
19		−	+						
20		−	+						
21	0·3 c.cm. Emulsion + 0·2 c.cm. Serum C.P.	+							
22		+							
23		+							
24		+							
25	0·3 c.cm. Emulsion + 0·2 c.cm. Serum B.	+							
26		+							
27		+							
28		+							
29	0·3 c.cm. Emulsion + 0·2 c.cm. Serum A.U.	+							
30		+							
31		+							
32		+							
33	0·3 c.cm. Emulsion + 0·2 c.cm. Serum B.A.	+							
34		+							
35		+							
36		−	+						

TABLE XXIV.

Case XXIV: Septic Abortion.

14/9/31. Hæmolytic streptococcus isolated from blood.
Virulence and protection tests carried out on September 17, 1931.

No. of Mouse.	Dose Given.	Days of Observation.				Remarks.
		1	2	3	32	
1	0·3 c.cm. Emulsion.	+				
2		+				
3		+				
4		−	+			
5	0·03 c.cm. Emulsion.	−	−	−	+	
6		−	−	−	−	Killed at end of 6 weeks. *Post mortem*, liver abscess (streptococci).
7		−	−	−	−	Killed at end of 6 weeks. *Post mortem*, N.A.D.
8		−	−	−	−	
9	0·3 c.cm. Emulsion +	+				
10	0·2 c.cm. N.H.S.	+				
11		−	+			
12		−	+			
13	0·3 c.cm. Emulsion +	+				
14	0·2 c.cm. Serum A.C.	−	+			
15		−	−	−	−	Killed at end of 6 weeks. *Post mortem*, both showed abscess in wall of peritoneum.
16		−	−	−	−	
17	0·3 c.cm. Emulsion +	+				
18	0·2 c.cm. Serum C.	+				
19		+				
20		−	−	+		
21	0·3 c.cm. Emulsion +	+				
22	0·2 c.cm. Serum A.U.	+				
23		−	+			
24		−	+			
25	0·3 c.cm. Emulsion +	+				
26	0·2 c.cm. Serum A.A.	+				
27		−	+			
28		−	+			

All these mice were injected with the same strain. Where serum was used in treatment it was administered with the strain, the whole being given intraperitoneally.

The 50% death time of the mice receiving the standard dose of emulsion without any serum was

TABLE XXV.

Martin.

18/11/28. Pneumococcus Type I isolated from sputum.
Virulence and protection tests carried out on November 21, 1928.

No. of Mouse.	Dose Given.	Days of Observation.			Remarks.
		1	2	3	
1	0·00001 c.cm. Emulsion. I.P.	−	+		
2		−	+		
3	0·0001 c.cm. Emulsion. I.P.	−	+		
4		−	+		
5	0·001 c.cm. Emulsion. I.P.	−	+		
6		−	+		
7	0·01 c.cm. Emulsion. I.P.	−	+		
8		−	+		
9	0·1 c.cm. Emulsion. I.P.	−	+		
10		−	+		
11		−	+		
12		−	+		
13	0·1 c.cm. Emulsion +	−	+		
14	0·2 c.cm. N.H.S.	−	+		
15	I.P. (C.S.L.)	−	+		
16		−	+		
17	0·1 c.cm. Emulsion +	−	−	−	Killed at the end of 6 weeks. *Post mortem*, N.A.D.
18	0·2 c.cm. anti-pneumo. Type I serum. I.P. (C.S.L. 1,160.)	−	−	−	
19		−	−	−	
20		−	−	−	

TABLE XXVI.

Case XXII: The Effect of Serum from Six Normal Horses and of Concentrated Antistreptococcal Serum on Pathogenicity of Strain "Deveney".

Virulence and protection tests carried out on November 5, 1931.

No. of Mouse.	Dose Given.	Days of Observation.											Remarks.
		1	2	3	4	5	6	11	12	18	19	32	39	
1	0·3 c.cm. Emulsion. I.P.	+												
2		−	−	−	−	−	−	−	−	−	+			
3		−	−	−	−	−	−	−	−	−	−	+		
4		−	−	−	−	−	−	−	−	−	−	−	−	Killed at end of 6 weeks. *Post mortem*, N.A.D.
5	0·3 c.c.m Emulsion +	−	+											
6	0·2 c.cm. N.H.S.	−	−	+										
7	I.P.	−	−	+										
8	I.	−	−	−	−	−	−	−	−	−	+			
9	0·3 c.cm. Emulsion +	+												
10	0·2 c.cm. N.H.S.	−	−	+										
11	I.P.	−	−	−	−	−	−	−	−	−	−	−	+	
12	II.	−	−	−	−	−	−	−	−	−	−	−	−	Killed at end of 6 weeks. *Post mortem*, N.A.D.
13	0·3 c.cm. Emulsion +	−	−	−	−	+								
14	0·2 c.cm. N.H.S.	−	−	−	−	−	−	−	−	−	−	+		
15	I.P.	−	−	−	−	−	−	−	−	−	−	−	+	
16	III.	−	−	−	−	−	−	−	−	−	−	−	−	Killed at end of 6 weeks. *Post mortem*, N.A.D.
17	0·3 c.cm. Emulsion +	+												
18	0·2 c.cm. N.H.S.	−	+											
19	I.P.	−	−	−	−	−	−	+						
20	IV.	−	−	−	−	−	−	−	+					
21	0·3 c.cm. Emulsion +	+												
22	0·2 c.cm. N.H.S.	+												
23	I.P.	−	−	−	−	−	−	−	−	+				
24	V.	−	−	−	−	−	−	−	−	−	+			
25	0·3 c.cm. Emulsion +	+												
26	0·2 c.cm. N.H.S.	−	−	+										
27	I.P.	−	−	−	+									
28	VI.	−	−	−	−	−	+							
29	0·3 c.cm. Emulsion +	−	−	−	+									
30	0·2 c.cm. Concentrated Antistreptococcal Serum. I.P.	−	−	−	−	+								
31		−	−	−	−	−	−	+						
32		−	−	−	−	−	−	−	−	+				

nineteen days. When this standard dose was administered with the various normal sera, the 50% death time was three, three, thirty-two, two, one and three days respectively, so that five of the sera, judged by this standard, were associated with the hastening of death of the experimental animals, while one serum only was associated with its delay.

If, instead of considering the 50% death time, the average death times of the second and third animals are considered, the same result obtains. Five sera are associated with a shortening of life, and only one with its prolongation. The shortening is very definitely marked with four of the sera, but with one of the five sera, namely, number 2, it is not so marked by this method of calculation.

We hope to repeat this experiment with larger numbers of mice to ascertain the exact measure of its correctness.

From time to time our work has been greatly hampered by the extreme difficulty of obtaining suf-

TABLE XXVII.

Case XXVII: Cellulitis of Leg.

14/8/29. Hæmolytic streptococcus isolated from blood.
Virulence and protection tests carried out on August 16, 1929.

No. of Mouse.	Dose Given.	Days of Observation.						Time Taken for Half the Animals to Die.
		1 17/8/29	2	3	4	5	6	
29	0·3 c.cm. Emulsion.	−	−	+				5 days.
30		−	−	−	−	+		
31		−	−	−	−	+		
32		−	−	−	−	−	+	
33	0·1 c.cm. Emulsion.	−	−	−	−	+		
34		−	−	−	−	−	−	
35		−	−	−	−	−	−	
36		−	−	−	−	−	−	
37	0·3 c.cm. Emulsion +	−	+					2 days.
38	0·2 c.cm. Serum C.P.	−	+					
39		−	−	+				
40		−	−	−	+			
41	0·3 c.cm. Emulsion +	+						1 day.
42	0·2 c.cm. Serum B.	+						
43		−	+					
44		−	−	−	+			
45	0·3 c.cm. Emulsion +	+						3 days.
46	0·2 c.cm. Serum A.U.	−	−	+				
47		−	−	−	+			
48		−	−	−	−	−	−	
49	0·3 c.cm. Emulsion +	+						2 days.
50	0·2 c.cm. N.H.S.	−	+					
51		−	−	−	−	+		
52		−	−	−	−	−	−	

TABLE XXVIII.

Case XXVIII: Mastoiditis.

5/12/29. Pure streptococcus isolated from blood culture.
Virulence and protection tests carried out on December 6, 1929, at 5 p.m.

No. of Mouse.	Dose Given. (Intraperitoneal Injection.)	Days of Observation.										
		1 7/12/29	2	3	4	5	6	7	8	9	10	14
1	0·2 c.cm. of centrifuged blood culture 24 hours old, suspended in saline 2000×10⁹ per c.cm.	−	+									
2		−	+									
3		−		+								
4	0·2 c.cm. culture suspension +0·2 c.cm. normal horse serum (no antiseptic).	−	+									
5		−	+									
6	0·3 c.cm. Emulsion + 0·2 c.cm. Serum C.P.	−	−	+								
7		−	−	+								
8		−	−	−	−	−	−	−	−	+		
9	0·3 c.cm. Emulsion + 0·2 c.cm. Serum B.	+										
10		−	−	−	−	−	−	−	−	−	−	−
11		−	−	−	−	−	−	−	−	−	−	−
12	0·3 c.cm. Emulsion + 0·2 c.cm. Serum A.C.	−	−	−	−	−	−	−	−	−	−	−
13		−	−	−	−	−	−	−	−	−	−	−
14		−	−	−	−	−	−	−	−	−	−	−

ficient mice of standard weight so that we might secure a high degree of exactitude in our results.

We should very much like to have been able to make our unit number of mice for determining each point eight or even twelve, but the small number of mice available and the large number of sera to be examined made this impossible.

Where the results with any single group of animals are not uniform and striking, we record them only as first approximations.

A series of nine strains were examined by a different technique. The organisms were centrifuged from tryptic digest broth and suspended in saline solution. The prophylactic dose of serum was given immediately before the inoculum of bacteria and both the injections were intraperitoneal. In this case, therefore, there was no mixing of serum and bacteria *in vitro* before administration, so that the direct effects of antiseptic on the organism could be discounted. The results obtained with the nine strains examined in this way are very similar to the results obtained in the examination of the strains from the twenty-four cases already recorded. On that account, therefore, only two illustrative tables are given. One deals with the strain from Case XXVII (see Table XXVII), where the standard dose of organisms took five days to kill 50% of the animals; whereas the animals which received antistreptococcal serum CP or antistreptococcal serum of either of two other well known brands, or normal horse serum, died much earlier. In the case of strain 28 (see Table XXVIII), on the other hand, the dose of culture caused the death of two out of three animals in two days, and a similar dose of culture preceded by a dose of normal serum was followed by death in two days in two out of two animals; whereas the antistreptococcal sera by two well known makers caused the survival of the bulk of the animals up to fourteen days. We have here, therefore, just as we had in the previous group, apparent benefit in one case and marked injury in the other, resulting from the administration of serum immediately before the dose of bacteria. The details of the other seven cases do not add any relevant facts to our inquiry.

Summary.

Two simple techniques have been tried for the discovery of the antistreptococcal serum which might be expected to benefit individual patients infected with particular strains of streptococci. The technique consists in one case in the therapeutic use of various sera to protect mice against the experimental infection with the strain isolated from the patient, and in the second case, the prophylactic use of serum for the same purpose. With both these methods we have found that the infected mice may, first, be unaffected by the exhibition of the serum; secondly, that they may in a few cases be benefited by the serum; or, thirdly, that they may be very definitely injured by it. The treated animals may die much more quickly than the untreated.

Conclusions.

1. Commercial streptococcal sera are not infrequently dangerous when they are used to treat experimental streptococcal infections of mice.
2. This dangerous effect may possibly be exerted in man, but before pressing the point the work recorded in this paper should be tested in several species.
3. At present we feel it is unwise to recommend streptococcal serum treatment in acute streptococcal infections in the human subject.
4. Commercial normal horse serum has also shown itself capable of aggravating the experimental streptococcal infections of mice.

Acknowledgements.

Our acknowledgements are due to Mr. Sutherland and to Mr. Hyams, bacteriological colleagues, who have most generously collaborated with us in times of difficulty.

Explanation of the Tables.

In the tables the positive sign means "death"; the negative sign, "still surviving"; f.d. = "found dead", and K. = "killed".

The days of observation start from the day after the inoculation.

Where no change in the mouse population under experiment occurred, the days of observation are frequently omitted from the tables for the sake of compactness.

The sera of the different makers are indicated by the letters A, B and C. When a maker makes more than one antistreptococcal serum, a second letter is used to indicate the type of serum.

AA represents scarlet fever antitoxin.
AC represents concentrated antistreptococcal serum.
AU represents antistreptococcal serum.
B represents antistreptococcal serum.
BA represents scarlet fever antitoxin.
C represents antistreptococcal serum.
CP represents antistreptococcal serum, Type II.
N.H.S. represents normal horse serum.

All the sera (except in a few instances of normal horse serum) contained antiseptic. Tricresol 0·3% and 0·4%, phenol 0·5%, chloretone 0·5% and chloroform 0·4% were used by the different makers.

The tables are numbered by the same numbers as those designating the cases from which the streptococci were isolated.

If tests were repeated, a letter is appended to indicate the repetition, for example, Table XXI followed by XXIA.

All repetitions were made with the original strain isolated.

On each table the source of the strain is indicated with the dates of isolation and of inoculation into the mice for test purposes.

In calculating the average time of death, fractions of a day have been taken as one day. If animals died during the night, they were entered in the records as having died after midnight, for no observations were made during the night.

In making the *post mortem* examinations only naked eye appearance was considered, except in a small percentage of cases where cultures were made, the results of which are reported on the charts.

In Cases VIII and IX the surviving mice were kept for two months, but no *post mortem* examinations were made.

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A NOTE ON THE PREPARATION OF INTRAVENOUS SOLUTIONS.

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AND
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THE use of intravenous therapy has increased of recent years; but all will admit that our knowledge of the more technical side of the preparation of intravenous solutions is meagre. Many fluids have been used intravenously, and in all probability their number will be extended; yet few, if any, precautions are taken to insure that anything approaching the pH value of blood is obtained. These various solutions are used in the treatment of patients who are very ill, and any sort of "reaction" must be to the disadvantage of the patient, and in certain instances may turn the scale, resulting in death. These reactions are of varying grades of severity, from a mild discomfort to a severe rigor, considerable elevation of temperature, circulatory collapse, and in some instances death.

A series of untoward reactions at the Melbourne Hospital awakened interest in these occurrences. Various substances were successively blamed. The purity of the glucose was naturally first questioned, the quality of the distilled water, the method of preparation of the solution, the method of sterilization, and the storage conditions.

Water.

In most hospitals sterile water is prepared by the condensation of steam. This steam is passed through pipes of various metals—copper, zinc, iron *et cetera* are all involved. Sterile distilled water is notoriously an unstable product, rapidly becoming acid in reaction on standing, owing chiefly to the absorption of carbon-dioxide, soluble to the extent of 0·3%, from the atmosphere. After repeated experiments it was found necessary to use fresh doubly distilled water prepared in an all glass still. No other method of preparation was found satisfactory.

Glucose.

The glucose was a source of great difficulty. Various qualities from various manufacturers were tried, and finally extra pure anhydrous glucose, specially prepared for intravenous injection, of the standard known technically as "U.S.P.X.", was obtained. Even glucose of slight impurity deteriorates so rapidly on keeping that it was felt necessary to insist on this grade, despite its high price.

Buffering.

Solutions of glucose, however carefully prepared, however pure the glucose, and whatever method of sterilization is used, rapidly become acid. In a few hours the pH value may fall to less than 5·0, and this is a very potent cause of undesirable reactions.

It was found necessary to buffer our solutions, and after experiment, sodium phosphate was selected as approximating to the normal body mechanism controlling the reaction of the blood stream. After a glucose solution has been made under aseptic conditions, it is allowed to cool and the solution is immediately buffered by the addition of di-sodium-hydrogen-phosphate to give a hydrogen ion concentration value of 7. For example, 50 cubic centimetres of 50% solution of glucose require 0·09 gramme of di-sodium-hydrogen-phosphate. Other solutions require approximately the same percentage of buffer.

Sterilization.

The routine method of sterilizing intravenous solutions at the Melbourne Hospital was to autoclave a flask containing the fluid under steam pressure. It was early noticed that such solutions became dark in colour, this being particularly noticeable in concentrated glucose solution, the cause being caramelization of the dextrose. Glucose suffers decomposition into glucogen, and at high temperatures yields caramel. Further, steam sterilization under pressure entails some danger of the absorption of minute amounts of metals carried over in the steam, and certain investigators have suggested that copper, nickel *et cetera* are responsible for some reactions. Therefore, after experiment, it was found that the most satisfactory method was to manufacture the solutions under strictly aseptic conditions, filtering the final product through sterile gauze, and finally sterilizing by boiling for fifteen minutes.

Storage of Solutions.

In a large hospital there must always be on hand for immediate use stocks of the various solutions. At the Melbourne Hospital these are now stored in a special emergency cupboard, asbestos lined to give a uniform low temperature, and directly under the supervision of the Chief Dispenser. Each bottle of solution is dated when made, and is checked at weekly intervals. Glucose discarded as unfit for intravenous use may still be used for rectal injection and need not be wasted. Our solutions are stored in glass bottles with glass stoppers, closely fitting, and sealed by covering the stopper with waterproof bilroth.

Sodium Chloride Solutions.

The above precautions have been mainly used in the preparation of glucose of strengths varying from 5% to 50%, but a solution of sodium chloride for intravenous use should also be made with great care. Chemically pure sodium chloride is used. The normal or physiological solution should not only contain that amount of salt necessary to make it isotonic with the blood, but should also have the same hydrogen ion concentration.

Our procedure here is to make a normal solution of sodium chloride with fresh doubly distilled water, and after sterilization check it when cool to the same hydrogen ion concentration as the blood, giving a pH value of 7·4, using, if necessary, sufficient di-sodium-hydrogen-phosphate. Of course, hypertonic and hypotonic solutions are similarly buffered, and the advantage of adding calcium salts to hypotonic solutions for use with grossly dehydrated patients is too well known to require more than mention.

Sodium citrate used for blood transfusion also varies in pH value, and it is therefore advisable to use the chemically pure neutral salt which, when freshly prepared with distilled water, has a pH value of 7.

Summary.

In conclusion, the position may be summarized as follows:

1. Intravenous therapy should not be entered upon lightly without a full knowledge of its dangers and the precautions to be taken.
2. Fresh doubly distilled water, prepared by all-glass distillation, should be used.
3. Chemically pure substances, particularly glucose, of very high standard must be insisted upon.
4. Sterilization of solutions by open boiling on an electric heater is the most satisfactory method, fifteen minutes being suitable for most solutions.
5. The solutions should be buffered after sterilization by the addition of a sterile solution of di-sodium-hydrogen-phosphate sufficient to give a pH value of 7.
6. Solutions should be freshly prepared, but if stock solutions are necessary, they should be checked at frequent intervals and stored at a uniform low temperature in the dark.

MODERN TREATMENT AS APPLIED TO POST-OPERATIVE PULMONARY COMPLICATIONS AND ACCIDENTS OF THE BEACH.

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AT first sight post-operative pulmonary complications and beach injuries do not appear to have much connexion with one another, yet in the treatment of most of the former and some of the latter there has been introduced of recent years a method of treatment of very great help. It is for that reason that I group the two in the one article, though in some respects they have nothing in common.

Post-Operative Pulmonary Complications.

Post-operative pulmonary complications are common, particularly after upper abdominal operations, though to a less extent after operation on any part of the body. They occur after local as well as after inhalational anæsthesia, perhaps not to such a great extent. For years they have been the subject of inquiry and research; embolism with resultant

infarct has been one of the many causes blamed. Certain it is that the upper abdominal operations have carried the greatest risk of these complications (apparently due to a reflex immobilization of one or other domes of the diaphragm); a previous attack of pneumonia has also been noted as a likely predisposing cause; naturally, the existence of any inflammation of the respiratory tract (such as bronchitis, laryngitis, or even a common cold) has always been considered sufficiently serious to warrant postponement of the operation.

Until I read Coryllos's article on "Post-Operative Pulmonary Complications and Bronchial Obstruction"[1] I had no clear and satisfying conception of the pathology of the condition. He is convinced that the determining factor in the production of this condition is the more or less temporary "plugging" of a bronchus by mucus which is followed by the absorption of the alveolar air and atelectasis of the corresponding portion of the lung. Even very thin mucus may be able to obstruct a bronchus when the lungs are at a disadvantage, as they often are after operation (because of the suppression of the cough reflex by narcotics, pain, posture), after injuries to the thorax or because of general weakness in wasting illnesses, in bedridden patients *et cetera*. Upon this condition pneumonic consolidation supervenes; in nearly every case apparently due to pneumococcus Group IV (normally present in the mucosa of the mouth and throat). If the obstructing mucus is infected with pyogenic organisms, suppuration may follow, if the obstruction is prolonged.

These are, very briefly, his views. If these are correct, then measures directed towards the early removal of the obstructing mucus are indicated. Such are: (*a*) change of posture, to encourage slight coughing to expel the mucus; (*b*) the use of expectorant mixtures; (*c*) avoidance of too many narcotics; (*d*) liquefaction of the mucus and toxic action on the pneumococci by inhalation of carbon dioxide (by producing hyperventilation of the lungs it provides the alveoli with the necessary amount of air for the expulsion of intrabronchial secretion); (*e*) in rare cases removal of the "plug" by means of the bronchoscope.

For over twelve months I have acted on these assumptions in patients under my care in private hospitals, and more particularly in Sydney Hospital, where the opportunities are more frequent.

My first case in Sydney Hospital was that of a man who developed pneumonia after an appendicectomy operation. My inquiries from the Fire Brigade Headquarters about Henderson and Haggard's inhalator (as used by the fire brigades in the United States) put me on immediately to a "traveller" from the States for a similar apparatus—the Bullard-Davis inhalator. It was fixed up very compactly in an arrangement like a suitcase. We had the cylinder filled from the Commonwealth Oxygen Company with oxygen 95%, carbon dioxide 5%, and gave this to the patient *viâ* a mask for five minutes every two hours. Clinical and radiological signs of pneumonia in the right lower lobe were definite prior to the treatment. Immediate improvement ensued upon the inhalations. In several days he was nearly well. Bacteriological investigation of the sputum revealed in this, as well as in all subsequent successful cases, pneumococcus Group IV.

The result of this case led to the purchase by the fire brigade authorities of this apparatus for the treatment of asphyxia, carbon monoxide poisoning *et cetera*.

As at Sydney and Saint Luke's Hospitals we already had a very efficient oxygen apparatus, made somewhat after the design of the one featured by Whitridge Davies in *The British Medical Journal* of November 19, 1927, it needed only the cylinder of oxygen and carbon dioxide to be placed alongside the oxygen cylinder already there, the rest of the apparatus being common to both. The percentage of carbon dioxide has been five, but anything up to 10% may be used. The mixing of the gases is done at the factory, not at the hospital.

I have used it for cases of post-operative bronchitis and pneumonia with the very greatest success. The only failure was in a post-operative case of bronchopneumonia (bilateral) with pyogenic organisms and influenza bacilli in the sputum (and subsequently in the patches of bronchopneumonia *post mortem*).

I have also used it to "wash out" the lungs after an upper abdominal operation when I had reason to fear pneumonia might ensue, also with success. But the number of cases in which it was so employed are too few to base conclusions upon.

Accidents of the Beach.

Perhaps the most common accident is asphyxia after immersion. Most of the patients recover after an intelligent application of the Schafer method of artificial respiration. But I am inclined to doubt whether the instructors of the various life-saving classes around Sydney emphasize sufficiently the importance of getting most of the water out of the lungs before getting air in; and how all-important is posture, in other words, the application of dependent drainage. The most rapid way of effecting the removal of the water would be to seize the patient by the feet and hang him upside down over the shoulders, but this requires some strength.

The next most effective way is to make use of the slope of the beach—the steeper the better—the head, of course, being downwards.

The artificial respiration after the Schafer method may then be proceeded with.

In spite of these measures, some patients are lost, and a perusal of a recent article by Henderson on "Resuscitation from Asphyxia" indicates how wide is the scope for the application of carbon dioxide. The mask, or nasal catheter, attached to the apparatus could be applied to the face, even while artificial respiration is in progress, but it is likely (so stimulating is the action of carbon dioxide on respiration) that the Schafer method would not have to be proceeded with for long.

The experience in American cities, where resuscitation from asphyxia by means of carbon dioxide is more common, is that after a short but intense asphyxia the effects are extraordinary; after longer, though less intense, asphyxiation, resuscitation is not so rapid.

It has another beneficial effect, namely, the prevention of the subsequent development of pneumonia. This, to my knowledge, was the cause of death in at least one case resulting from the well known steamer *Greycliffe* disaster.

It will be urged, I know, that such a course of procedure is visionary and impracticable, but the apparatus as used by the Sydney Fire Brigade is embodied in a suitcase and is quite portable. A cheaper one can well be made locally. Human life is sacred and no efforts should be too great to save it.

Henderson quotes Sir Michael Foster as having said that it is rarely possible to carry a physiological discovery "bleeding from the laboratory to the bedside". This is very true, for the application of the therapeutic uses of carbon dioxide has reached very few Sydney bedsides. I tremble to think how long before it will reach the beaches.

An occasional accident on the Sydney beaches is shark bite. In this again I do not think we are applying our knowledge of the treatment of shock gained by experience in the accident wards of a civil hospital, and to an even greater extent on the battlefields of the Great War.

The usual procedure at present is to hurry the victim of a shark bite in his wet bathing clothes in an ambulance for a distance of five or six miles over more or less rough roads. My view is that death from shock is the most potent cause of the large mortality in these cases. Any hæmorrhage could be dealt with in the surf shed by the application of artery forceps, applied by a local medical man. After their application, the tourniquet could be released.

I do not see why provision could not be made in the local life-savers' shed for the patient to spend eight or twelve hours or more under the care of a trained nurse and a visiting doctor. Shock having been combated, he could later be moved to a general hospital. I do not think the very slight risk of gas gangrene ensuing is sufficient to justify an early amputation.

I will be told the scheme is impracticable. To that I have already given an answer.

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Reports of Cases.

DIABETIC PSEUDOPARESIS.[1]

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THE patient, M.S., is a woman aged fifty-seven years. She is married and has four children. Her father died at forty years of age from peritonitis. Her mother, who is alive and healthy at seventy-six, had twelve children, two by the first marriage and ten by the second. Eight step-brothers are alive and well, and two step-sisters. One brother died, aged fifty, from pneumonia. One step-brother is regarded as being somewhat abnormal mentally; he talks at random and is excitable, and another step-brother had an attack of melancholia, but recovered.

The patient is the eldest of twelve children. Her infancy was healthy, though she had the usual childhood complaints. She left school at eleven and helped with housework at home until thirteen, when she became a machinist in a boot factory until her marriage at seventeen. Her early married life was unhappy, as her husband left her alone a great deal, but during the past ten years he has been much more considerate. She has always been nervous and excitable, reserved and quiet, but easily annoyed. She has few friends and no particular interests. The menopause occurred at fifty. She has had no serious illnesses. She had herniotomy fourteen years ago and has been subjected to curettage of the uterus on several occasions. She has four children, aged thirty-eight, thirty-six, twenty-six and twenty-two. All are healthy, but "highly strung". Since the patient's admission a daughter has had an acute mental breakdown. One child was still-born when the patient was forty-three years of age. This was her last pregnancy. She had frequent miscarriages after the birth of her second child. She admits occasional potus, but denies venereal disease.

She has been affected for about thirteen years. She lacked energy and became progressively more dull. She attended South Sydney Hospital for two years at that time because of the onset of the climacteric. She managed to carry on fairly well at home until eighteen months ago, when she lost interest in everything. She attended the out-patient department at Sydney Hospital and is said to have had three injections into her arm. Her daughter believed that she was worse because of this and took her to a "quack" who treated her for three months by electricity without benefit. During the past few weeks she has become much worse and she began to express delusions that her neighbours were running about unclothed and that she could hear screaming and could see a woman in a shroud. Her memory became impaired and she was depressed, morbid, drowsy and disinterested, rather childish and had to be washed and dressed. She attempted to leave the house and wander away. She complained that her legs were weak, and although walking fairly well, she dragged her feet.

On admission she was incoherent and almost unintelligible in speech and quite incapable of giving any connected account of herself. Her speech was slurred and "thick". There was considerable impairment of memory and orientation. She lay in bed in a dull, apathetic and listless condition, entirely unresponsive to her environment, at times becoming restless in an aimless way. She exhibited considerable affective deterioration and was childishly dependent and lacking in initiative. She had hallucinations of hearing and of vision.

On examination she was a stout woman of dull appearance with heavy growth of hair on her face. Her systolic blood pressure was 160 and her diastolic pressure 105 millimetres of mercury. The heart sounds are distant. The respiratory and alimentary systems are clear. The urine has a specific gravity of 1·026, it is amber coloured, its reaction is acid, it contains no albumin or pus. It gives a green reduction with Benedict's solution. Benedict's quantitative test reveals 0·2% sugar. Microscopically a few bladder squames, pus cells and calcium oxalate crystals are found.

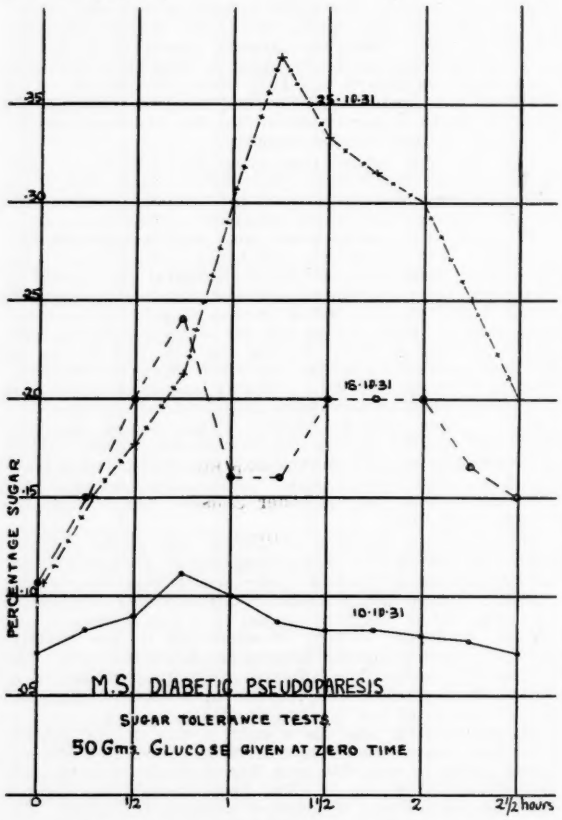
On examination of the nervous system the face is seen to be expressionless and there is a suggestion of paresis of the right side. The lips and tongue are tremulous, speech is slurred. The tongue deviates slightly to the right. The fundi are clear. The pupils react normally. There is no obvious disturbance of sensation. There is general loss of tone of muscles, with weakness. The patient walks with her eyes on the ground and has a tendency to shuffle, and there is absence of associated movements of the right upper extremity in walking. The knee jerks are absent. The plantar responses are flexor.

[1] The patient described herein was shown at a meeting of the Section of Neurology and Psychiatry of the New South Wales Branch of the British Medical Association on November 19, 1931.

The blood serum gives no reaction to the Wassermann test. The cerebro-spinal fluid is normal throughout.

An investigation of the glycosuria showed the presence of sugar in the urine with as low a blood sugar content as 0·07. A sugar tolerance test was carried out on October 10, 1931, the result being a normal curve (see diagram). It is to be noted that, although the blood sugar content did not rise above the normal threshold, there was glycosuria, the maximum concentration of 1·66% being reached in the urine voided two hours after the ingestion of 50 grammes of glucose. At this period repeated examinations in the fasting state gave blood sugar values of 0·07, 0·07, 0·07, 0·08.

To endeavour to reduce the blood sugar content to determine the actual threshold, the patient was given an entirely meat diet. Paradoxically there was a gradual increase in the blood sugar content in the fasting state, the figures 0·094, 0·10, 0·107 being obtained. A second sugar tolerance test was done on October 18, the curve (see diagram) on this occasion being definitely of the diabetic type.



Acetone bodies appeared in the urine ten days after the commencement of the meat diet.

A third sugar tolerance test was done on October 25 and was of severe diabetic type.

Ordinary diet was resumed and acetone bodies disappeared from the urine, but a slight glycosuria persists.

Comment.

Diabetes, if the terminal confusional and comatose states are excluded, is not a common cause of psychosis. Diabetic pseudoparesis, to which category this case conforms, is rare. Kraepelin mentions the syndrome. Sluggish or inactive pupils may make the resemblance to general paralysis even greater. In the absence of vascular degenerative changes considerable improvement may be anticipated from treatment.

Reviews.

OSTEOPATHY.

"MANIPULATION AS A CURATIVE FACTOR" has been designed by the author, Ethel Mellor, to give information to the thoughtful lay and medical section of the community on the manipulative treatment of disease in certain conditions of the spine and limbs.

Four chapters, covering ninety pages, are devoted to an excellent historical review, including many quotations from medical works, in an attempt to trace the genesis of the modern practice of osteopathy. However, this portion of the work is not so convincing a proof of the value of osteopathy as the author appears to think. What medical practitioner would think of basing his treatment of any infectious fever today on the views expressed in medical literature current hundreds of years ago, or where would modern surgery be if the practice of this art were based on pre-Listerian conceptions? The author surely claims too much when she writes:

> Osteopathy covers all fields of the art of healing, as does orthodox medicine. All diseases of the mind and body come within its scope—mental and nervous, acute and chronic, contagious and non-contagious, gynæcology or the diseases of women, obstetrics or midwifery, general and special surgery. There is no disease and no disturbed condition of the mind or body that osteopathy does not recognize. It also recognizes and includes preventive medicine. Osteopathy is a system of healing and not a panacea or universal remedy.

She is apparently sincere in this belief inasmuch as she claims by implication that a tuberculous joint was healed because it was not manipulated, in spite of the desires of the patient; but she does not attempt to recognize the need for rest in the treatment of tuberculosis. The whole subject is treated with the outlook of a writer on popular medicine rather than that of the scientific investigator. The term "lesion" is used very frequently, and it is difficult to know from the text precisely what is implied by this term. On page 204 the author writes:

> The keystone of osteopathy in theory and practice is the diagnosis of the spinal lesion and its correction by manipulation. A spinal lesion is a tender area, affecting one or more adjacent vertebræ, with limited motion and contractured deep muscles. Writers and research workers have shown the coexistence of other parts of the body receiving their nerve supply from the involved spinal region.

This is the most definite statement we have been able to find. Although practically every disease to which the body is subject is mentioned as receiving benefit from manipulation, the description of the mechanism by which improvement takes place is so vague and loose that it carries no conviction.

In a summary the author attempts to correlate medicine and osteopathy as systems of healing, and arrives at the conclusion that the one difference between the two systems is the domination of drug medication in medicine and spinal manipulation in osteopathy. We cannot refrain from arriving at the conclusion that the author has been sadly misled in her views regarding the practice of modern medicine. Apparently most of her knowledge has been derived from a very intensive research into ancient medical literature, and she has not imbibed the scientific spirit which today is such a driving force in the study of modern medicine. Her conclusions regarding the value of osteopathy leave the reader entirely unconvinced and are arrived at without any arguments to connect the facts she quotes and the conclusions she deduces from them.

[1] "Manipulation as a Curative Factor: Osteopathy and Medicine, with an Appendix on Hay Fever", by E. Mellor; 1931. London: Methuen and Company, Limited. Demy 8vo., pp. 268, with illustrations. Price: 10s. 6d. net.

The Medical Journal of Australia

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"AVERTIN."

A YEAR or two ago reference was made in these columns to anæsthetists and anæsthetics and to the precautions that should be taken and to the tests that should be carried out before an anæsthetic is given. Protests were made, though not through the medium of this journal, that the performance of elaborate tests before administration of an anæsthetic is not always possible, at least in general practice, and it was held that the setting up of a high standard in a journal such as this would act prejudicially in the event of an unexpected death under anæsthesia. Everyone will recognize that it is not possible in every instance to carry out many tests before an anæsthetic is given. At the same time everyone knows that some preliminary tests are necessary, everyone knows that it is easy to become careless, and every medical practitioner knows that the preliminary examinations made by some anæsthetists are at times perfunctory. A year or two ago a statement was necessary. In view of the occurrence of deaths following the administration of "Avertin" the attention of anæsthetists must again be claimed.

Tri-brom-ethyl alcohol or "Avertin" is a powerful drug. The German chemists who put it on the market recognized its potency and carried out much experimental and clinical work with it before they made it available to practising members of the medical profession. They called it a basal anæsthetic, and they sold it as a basal anæsthetic. It must therefore be used as a basal anæsthetic and nothing more. When it is used as a basal narcotic it is sometimes found that other anæsthetics, such as gas and oxygen, are unnecessary. But too much emphasis cannot be laid on the statement that the man who sets out to produce complete narcosis with "Avertin", whether the patient has satisfied all possible tests preliminary to anæsthesia or not, is taking an unjustifiable risk and is asking for trouble. The standard doses are laid down and should not under any circumstances be exceeded. Further, "Avertin" must not be given, even in small doses, to a patient who may be described in clinical jargon by that horrible term "a bad anæsthetic risk". In other words, before "Avertin" is given, its would-be users must make themselves familiar with its pharmacology—they must know just what can be expected of it and must appreciate its dangers.

Deaths following the administration of "Avertin" may or may not be due to the drug. On more than one occasion "Avertin" has been blamed, and careful inquiry has revealed another cause of death. It is possible that in some of these cases death would sometimes have occurred whether "Avertin" had been used or not, and in these circumstances it would have been wiser to have used some other form of anæsthesia. All deaths following administration of "Avertin" should be reported in full in a medical journal. In these reports the patient's condition before operation should be described in detail, the reasons for the use of "Avertin" should be given, and the method of calculating the dose should be described. In one large hospital several deaths have occurred after the administration of "Avertin". In response to a suggestion that these deaths should be reported, an unofficial reply has been received that a report would be made only if other hospitals reported fatalities. This attitude is to be deprecated; it is almost an admission that there is something to be concealed. Further, *post mortem* examination should be carried out on all persons

who die while under the influence of "Avertin". It is not sufficient for a coroner to express the opinion that adequate steps were taken to bring about the recovery of the patient and that no blame is attachable to anyone. Only by the most careful scrutiny of clinical and *post mortem* records will more be learned about "Avertin" and similar drugs. That anæsthesia can be produced without untoward incident in, say, ninety-nine cases out of a hundred, is not sufficient; the fatalities must be eliminated.

Current Comment.

PROTEIN THERAPY.

IT is interesting to go back nearly twenty years in the history of the study of practical immunity and to realize that non-specific therapy was employed so long ago. As early as 1916 chronic infective arthritis was treated by injections of non-specific bacterial protein (typhoid vaccine). Since that date the method has been widely extended in application and employed for a variety of conditions, including diseases of the eyes and the skin, chronic infections, certain manifestations of syphilis, and obliterative vascular disease. It is not surprising, therefore, that a considerable literature exists on the subject and that a need should be felt for careful study of the indications for so potent a therapeutic agent, and also its limitations and reactions.

An excellent summary of the literature is given by P. S. Hench[1] in an article on the usual and unusual reactions to protein therapy, in which he also reviews the record of 10,000 such injections given in the services of the Mayo Clinic. The patients studied were under treatment either for arthritis (1,500 cases) or other conditions, chiefly vascular (1,000 cases). The protein used was in most cases the triple typhoid preparation known familiarly in Australia as "T.A.B. vaccine", and the route chosen was nearly always the intravenous, this giving sharper and prompter reactions.

Hench distinguishes three phases in the usual reaction. The prodromal phase consists of a more or less definite chill and perhaps slight local reaction. In three to five hours after the injection occurs the first or "negative" phase in which the temperature rises, and there is an increasing focal reaction at the site of the lesion. The second or "positive" phase comes six to twenty-four hours after the injection, with a falling temperature and a dwindling focal reaction leading to a variable degree of euphoria. Occasionally secondary temperatures and chills were observed on the second day.

These may be regarded as the reactions to be expected and aimed at, and most observers will agree that the best response is obtained when there has been an adequate negative phase. But in addition to these obvious clinical signs many other less evident physical and chemical changes have been observed, both in the human subject and the laboratory animal. These include alterations in the basal metabolic rate, in vasomotor mechanism, in various excretory and secretory activities, and in the composition and physico-chemical properties of the body fluids. How can the extraordinarily complex set of reactions be explained? And will such knowledge help us to understand unusual reactions when these occur?

Hench remarks that the postulation of some central mechanism makes comprehension easier, and refers to the work of Petersen, Muller and others, which suggests that injected protein is fixed in the cells of the reticulo-endothelial system, causing thereby a prolonged stimulation of the splanchnic organs (chiefly liver, bowel and spleen) and a dilatation of the splanchnic blood vessels, while there occurs a simultaneous depression in the activity of the skin and muscles and a constriction of the peripheral vessels. Both these states then undergo a reversal and eventually equilibrium is regained. This concept provides an explanatory basis for the usual reactions and prepares us for the occurrence of unusual reactions.

What are these unusual reactions? At the outset it may be said that untoward effects are uncommon; in the Mayo Clinic series these occurred only after 0·2% of all injections given, the patients affected constituting only 0·5%. The following diverse conditions are recorded: subacute pleurisy and pericarditis, nephritis, flaring up of other infected areas, such as lymph glands, infected gall-bladders, dental apical septic foci *et cetera*, ocular inflammations, such as inflammatory glaucoma, appendicitis (there having been previous attacks), enteritis, keratitis, and thrombosis in various blood vessels. One case is recorded in which acute nephritis and death from anuria followed the injection of twenty-five million dead typhoid bacilli. This patient, aged fifty-one, was under treatment for polyarthritis and was found at autopsy to be the subject of definite arteriosclerotic changes. It is pointed out that a few deaths have also been recorded in the literature as due to "anaphylaxis", but that the suggestion has been made that these are in reality more correctly to be ascribed to acute vasomotor collapse.

Schmidt and Petersen are quoted as classifying these accidents as stimulation of inflammatory foci of either infectious or non-infectious origin and stimulation of latent diathetic phenomena (such as asthma, epilepsy and *delirium tremens*). To these Hench adds accidents related to existing vascular disease.

This summary enables us to put our finger on the chief contraindications and risks of protein therapy. For, though vast numbers of patients have been subjected safely and often advantageously to this line of treatment, it is the medical practitioners' duty to appreciate the possibility of danger, and,

[1] *Archives of Internal Medicine*, January, 1932.

more important still, to avoid it. These contra-indications include pronounced arteriosclerotic vascular disease, definite degrees of cardiac failure, exhaustion states, pulmonary tuberculosis, states predisposing to bleeding, allergic conditions, and severe chronic infections and intoxications.

These conclusions are paralleled by Kemp and Stokes[1] who, in studying the use of bacterial proteins in syphilis, advise the exclusion of sufferers from cardiovascular disease, active pulmonary lesions and marked cachectic states. An interesting point concerns diabetics. It is agreed that acidosis in diabetics is a contraindication for protein therapy, but that otherwise it is well tolerated by them; though the blood sugar tends to rise, the rise is readily corrected by increasing insulin dosage or reducing carbohydrate intake.

Doubtless many practitioners employing this therapeutic method would be glad to learn more of its mechanism so that they might replace empiricism by more accurately calibrated knowledge, and still more to know that, although the reactions may be (to the patient at least) apparently somewhat drastic, the risks and accidents are rare. Even the most enthusiastic would not look for spectacular results in all cases, but the successes are sufficient to warrant a more extended use of a powerful weapon in the battle against disease.

THE PLUMMER-VINSON SYNDROME.

BRIEFLY the so-called Plummer-Vinson syndrome may be described as a complex of secondary anæmia, dysphagia, achlorhydria (frequently), glossitis, loss of appetite, debility, and nervousness. In 1914 Plummer recognized what he regarded as an hysterical dysphagia; in 1918 several observers noted that this peculiar type of dysphagia was associated with pathological changes in the œsophagus; in 1922 Vinson observed that secondary anæmia was a usual accompaniment of the condition. Many have held the view that the anæmia is secondary only to malnutrition resulting from anorexia and dysphagia; but latterly doubts have been cast on the validity of this theory. Hurst believes that the dysphagia is due to achalasia of the pharyngo-œsophageal sphincter, the result of degeneration of the vagus nerve endings in Auerbach's plexus. Witts sees between so-called simple achlorhydric anæmia and the Plummer-Vinson syndrome a relationship comparable to that between Addison's anæmia and subacute combined degeneration of the spinal cord.

Practically nothing is known of the ætiology of the anæmias. The therapeutic employment of liver extract and stomach extract has taught little; possibly it has even created some confusion. The ranks of the anæmias continue to increase and bid fair to outdo in magnitude the imposing lists of conditions once dubbed gouty. It is safe to assume that increased knowledge, particularly in regard to ætiology, will eventually effect a great reduction in the number, even if the term "anæmia" does not cease to be employed as the name of a disease. Meanwhile, descriptions of newly discovered anæmias and newly discovered symptoms must be patiently borne, for they are indicative of increasing knowledge and represent a groping after the truth which, in the fullness of time, must be laid bare to the light of day and the eyes of science.

George Graham and R. S. Johnson have recently drawn attention to a hitherto unrecognized symptom of the Plummer-Vinson anæmia.[1] They studied five patients who had practically all the known symptoms that go to make up the Plummer-Vinson syndrome, and one patient who had all the symptoms with the exception of dysphagia. The absence of dysphagia in one instance suggests that there may be some cause for the anæmia other than starvation. But can Graham and Johnson be sure that their sixth patient was really a sufferer from Plummer-Vinson anæmia? After all, in the first description of the syndrome, dysphagia was the symptom chiefly dealt with. However, it may be significant that this patient was the youngest in the series, and perhaps had not been affected long enough to allow the development of dysphagia.

An increase in the fragility of the red blood cells is known to occur in acholuric jaundice; it is indeed one of the distinctive features of this disease and has never been observed hitherto in any other condition. Graham and Johnson noted it in all but one of their six cases. In the exceptional case the patient had received a good deal of treatment and had improved greatly in health before the test was made. They conclude that the anæmia is not due to the ordinary causes of secondary anæmia and is not identical with the chronic microcytic anæmia described by Witts. They offer the suggestion that dysphagia, far from being an ætiological factor, is a late symptom of the disease. Other observers have noted that the condition of the blood improves immediately on the disappearance of the dysphagia. Graham and Johnson disagree with this observation and remark that no pronounced improvement occurs until treatment with liver or iron in large doses is instituted.

The test for increased fragility of the red blood cells is not often used in medical practice. It is a simple test, made by adding a suspension of washed red blood cells to saline solutions of varying dilution. Note is made of the strongest solutions in which partial and complete hæmolysis occurs. Fragility of the red blood cells requires further investigation. A careful study of this phenomenon might lead to the acquisition of considerable knowledge concerning the anæmias. If the views of Graham and Johnson in relation to the sequence of events in the development of the Plummer-Vinson syndrome are correct, diagnosis may be possible long before the appearance of dysphagia or the characteristic changes in the œsophagus.

[1] *The Journal of the American Medical Association*, May 25, 1928.

[1] *The Quarterly Journal of Medicine*, January, 1932.

Abstracts from Current Medical Literature.

RADIOLOGY.

Intrathoracic Lymphoblastoma.

B. R. KIRKLIN AND HANS W. HEFKE (*American Journal of Roentgenology*, November, 1931) review the literature and discuss Hodgkin's disease, lymphosarcoma, and leuchæmia. They consider a precise diagnosis of any one of these diseases cannot be made by means of X ray examination. Any of the three may exactly resemble either of the other two. The radiologist might sometimes be right if he considered bilateral involvement of the mediastinum with multiple discrete hilar nodes as being indicative of leuchæmia, or a large bilateral tumour as being indicative of lymphosarcoma, but either manifestation occurs just as often in Hodgkin's disease. All that should be expected of the radiologist is a broad diagnosis of lymphoblastoma, or malignant lymphoma, if the latter term is preferred. The authors note that radiological manifestations may be demonstrated in the thorax in about 50% of cases of Hodgkin's disease and in about 20% of cases of lymphosarcoma and of leuchæmia. Enlargement of the mediastinal and hilar nodes is the most common manifestation. Involvement of the lungs, either of the infiltrative or of the metastatic type, was found in 30% of the cases of Hodgkin's disease, in about 23% of the cases of lymphosarcoma, and in 40% of the cases of leuchæmia, whenever involvement of the thorax was demonstrable.

The Signs of Tuberculous Enterocolitis.

H. H. CHERRY (*American Journal of Roentgenology*, January, 1932) gives a review of the literature on tuberculous enterocolitis and discusses the condition very fully. He concludes that an accurate diagnosis can be made when the lesion is in the ileo-caecal region and that diagnosis becomes more uncertain when the lesion is situated proximal or distal to this. However, if there are intestinal lesions, one or more are sure to occur in the ileo-caecal region, and if the radiological and subjective signs are considered together, a large percentage of cases can be detected. Constipation is rarely a sign of intestinal tuberculosis. Pain and loose stools are the most common symptoms. The X ray evidence of the disease consists chiefly of hypermotility, persistent localized intolerance to barium (producing filling defects) and increase of intolerance on palpation. The author considers that, if after twenty-four hours the proximal half of the colon or all of the ascending colon, including the caecum, has been emptied, disease should be suspected. Indeed, any ulcerated segment of the colon is usually free of barium after twenty-four hours. The author considers that the opaque meal is of more value than an enema, especially in following the progress of a case. When healing occurs, the colon may in some cases return to its normal appearance, although the diseased segments usually remain a little constricted and less pliable than normal, due to cicatrization. The clinical manifestations disappear before the radiological signs.

Ear Complications of Cranio-Cerebral Injuries.

E. S. GURDJIAN (*Radiology*, January, 1932) emphasizes the seriousness of bleeding from the ear in cranio-cerebral injuries. He finds that in cases with unilateral bleeding or discharge of cerebro-spinal fluid, the mortality is approximately 38%, and if the discharge is bilateral the mortality rises to 67%. Careful X ray examination proved that over 95% of the patients with aural bleeding had a fracture somewhere in the skull; in many instances the fracture was in some part of the skull distant from the ear. A fracture line in the mastoid region, extending towards the vertex or the occipital bone, was found in fully 50% of cases; this was the commonest X ray finding. Fractures in the parietal bone, extending down into the middle fossa, were fairly common. In other instances there were fractures in the region of the *foramen magnum*, probably extending forward toward the petrous bone. A certain number of the frontal sinus fractures caused aural bleeding. A few compound and depressed fractures were accompanied by bloody discharge from the ear.

Nephroptosis and Urinary Stasis.

H. L. MORRIS (*Radiology*, January, 1932) deals at length with the anatomy, histology and physiology of the upper part of the urinary tract and then passes to the consideration of the factors pertaining to renal or ureteral stasis and the means of diagnosis. He insists that a fluoroscopic examination should be made while the opaque solution is filling the ureter and the pelvis and calyces of the kidney, in order that the motor function and physiological action of the kidney and ureter might be studied. The degree of respiratory excursion is studied, and also the actual amount of excursion when the patient is raised from the prone to the vertical position. It will be noted that many renal pelves readily empty, although there is an abnormal amount of motility with resultant tortuosity of the ureter. In the erect posture, should there be a delay in the emptying of the renal pelvis, the kidney can be elevated by pressure with the hand on the abdomen; the usual process of emptying can then be observed to continue. In another instance there may be little or no appreciable excursion of the kidney, and yet in the erect posture there is delay in emptying. This may be due to fixation of the upper part of the ureter, even a slight downward descent of the kidney being sufficient to prevent normal emptying. The author is of the opinion that the respiratory excursion of the kidney in the prone position is not a true index of the condition in the erect posture, and advises palpation of the kidney in both the prone and erect positions. Having noted the renal motility, the examiner must also decide whether there is any retention or interference with the normal emptying of the renal pelvis while the patient is in the erect posture, and whether the renal pelvis contracts and relaxes normally when the kidney is elevated by the hand. The examiner can thus decide with some degree of accuracy whether a patient should be subjected to nephropexy or whether he might be benefited by a suitable abdominal support.

Systemic Blastomycosis.

I. GASPAR, W. FEUSTEUMACHER AND G. GINGEMANN (*Radiology*, February, 1932) report in detail a case of systemic blastomycosis, and describe the X ray appearances of the lung and bone lesions. Radiological examination of the chest revealed a consolidation of the right upper lobe, which had the appearance of lobar pneumonia in an early stage of resolution. This gradually cleared, and at the last examination, made shortly before death, only a few lines of increased density radiating out from the hilum could be observed. The authors consider the lung lesion was the primary focus of infection. Practically every bone in the body was involved. The lesions were purely destructive throughout the course of the disease and were characterized by the lack of reparative and of periosteal reaction, clear-cut margins, their situation (in the cortex), lack of osteoporosis, multiplicity, rapid development, and accompanying sinuses. Blastomycetes were found in the lesions culturally and histologically. The authors conclude that there is no satisfactory treatment and that the mortality rate is approximately 100%.

PHYSICAL THERAPY.

Radiotherapy in Dry Gangrene.

A. ZIMMERN, J. A. CHAVANY AND R. BRUNET (*Journal de Radiologie et d'Électrologie*, July, 1931) quote eight cases, with coloured plates, showing the effect of radiation over the suprarenal areas in diabetic gangrene and in gangrene resulting from intermittent claudication and others forms of gangrenous extremities. They use 130,000 volts filtered through five millimetres of aluminium, and give four sittings, totalling in dosage 1,600 to 2,000 Solomon Röntgen units, repeated in eight to ten days. Relief from pain was noted in all cases, and in others the gangrenous appearance had completely gone and cicatrization had taken its place. Considering that the anatomical and functional relationship between the sympathetic and suprarenal system is intimate, the authors aim to irradiate not only the suprarenal glandular area, but also the splanchnic area, and so to obtain the

secretion from the adrenal glands to the exclusion of other functions of the organ, such as the elaboration of cholesterin.

Goître.

ALDEN H. WILLIAMS (*Radiology*, March, 1932) points out the variation of opinion in regard to the treatment of goître. Basing his views upon the theory of depressing a hyperactive gland function, he stresses the value of radiation treatment. He reports the results of treatment of 200 patients, observed over an extended period. On an average ten treatments were administered to each patient over a period of three and a half months. The average drop in pulse rate was 24·2 beats per minute. The average gain in weight was 3·6 kilograms (eight pounds), and lowering in the basal metabolic rate 23%. One hundred and sixty-one patients (80·5%) were definitely cured. Twenty-seven patients (13·5%) were improved, making a total of 188, or 94%, either cured or improved. Eight (4%) suffered from a recurrence after one year; five of these were later treated again and cured. Only two (1%) developed symptoms of hypothyreoidism and only one (0·5%) developed telangiectases. The importance of unhurried diagnosis and a frequent estimation of the basal metabolic rate is emphasized.

Hæmangioma: Some Observations on the Results of Radiation Therapy.

HUGO ROESLER (*American Journal of Roentgenology and Radium Therapy*, February, 1932) gives the indications for the methods of treating hæmangioma. The methods vary with the patient and with the location of the lesion. He states that much depends upon the size of the tumour, the age of the patient, the probable cosmetic results, and the possibility of bleeding. The report is based on a study of forty patients treated with various techniques and observed over periods up to seven years. Twenty-five were under two years of age, 34 were below twenty. The situations were as follows: Eyelids, 14; lips, 4; nose, 4; face and neck, 16; scalp, 2; other parts of the body, 4. In four cases the lesions were on two different parts of the body. In seven cases the size of the tumour measured up to four centimetres in diameter. In one-fourth of all cases there was a considerable extension into soft tissues beneath the skin. No extremely large tumours were found. Almost all cases corresponded to what is called "cavernous hæmangioma" and "*nævus vasculosus*". The average time which elapsed between the last treatment and the last observation was seventeen and a half months, the maximum being seven years. The treatment consisted in almost all cases in the application of radium. Only a few patients were treated by X rays. In the latter the radiation used was obtained with 200 kilovolts peak, four milliampères, filtered through a thickness of 0·5 millimetre of copper and 4·0 millimetres of celluloid at a distance of 50 centimetres. For radium treatment steel needles at 1·0 centimetre distance with a 1·5 milllimetre brass filter, in a dose of 250 to 300 millicurie-hours, were used at intervals of six to eight weeks. The results were definitely better in the treatment of younger patients. In the group of twenty-five patients below two years of age, the treatment of eighteen was followed by excellent results; five improved greatly during the period of observation of three months; in one case there was moderate improvement only fifteen months after the administration of a standard treatment of 250 millicurie-hours, which apparently was insufficient; another patient in this group was not followed. When the results in this group are compared with those in a group of children ten years of age and older (comprising ten patients), it is seen that the chances of healing and improvement in the latter group are not so striking. In this group there was an excellent or very good result in only three cases, four patients improved, two were not followed long enough to allow a definite statement, and one failed to improve. The latter patient received only one treatment, probably insufficient. In the treatment of these patients the smallest dose that will bring about improvement should always be used because of the better cosmetic results. It is probably unwise ever to use the full erythema dose.

Uterine Hæmorrhage.

DURING a period of eleven years J. H. Bridenbaugh (*Radiology*, February, 1932) has treated by radiological methods certain selected patients suffering from uterine hæmorrhage. He divides them into three groups. The first group consists of women under thirty-five years of age without tumour or other demonstrable pelvic disease, who resisted conservative treatment and continued to bleed excessively; all patients were promptly relieved of their excessive bleeding, and there were no unpleasant complications. The second group includes the patients who were near or past the usual age for the menopause, who had no demonstrable tumour or inflammatory disease to account for their hæmorrhage, but who continued to bleed excessively in spite of conservative medical management: their condition is commonly styled hæmorrhage of the menopause and is said to be due to fibromyoma of the uterus or metritis or endometritis; small doses of radiation are usually all that is needed; X rays and radium act equally well; one cycle of X ray therapy is usually sufficient. The third group is composed of patients suffering from fibromyoma. In this group there is still room for study and discussion as to the best mode of treatment. The author states that irradiation of myomata is the treatment of choice and, with careful diagnosis and selection of cases, offers the least risky way to recovery. Undoubtedly certain patients are best treated by surgical operation. In the border-line cases in which the complete diagnosis is in doubt, there will always be a divergence of opinion as to the best form of therapy. At the present time such divergence of opinion is great. One prominent gynæcologist states that the treatment of persons suffering from fibromyomata by X rays is useless and exercises a harmful effect on the general endocrine activity and metabolism. In deciding which type of patient is best operated on, it is generally agreed that very large, necrotic, or calcified tumours are best treated by surgical removal. Pedunculated submucous growths are at times resistant to radiation and may constitute an indication for surgery. Tumours of comparatively young women are best treated by surgery, if it is possible to preserve the major portion of the uterus. The author states that he has not, to his knowledge, treated any patients suffering from carcinoma under a mistaken diagnosis of myoma. A total of 309 patients suffering from uterine bleeding have been subjected to radiation treatment. In one instance complete failure resulted. In two cases the bleeding was controlled, but subsequent operation was necessary for removal of the tumour. Six patients discontinued treatment before a complete series had been administered. In 300 cases a satisfactory result was obtained.

Gynæcomastia.

JOHN G. MENVILLE (*Radiology*, February, 1932) states that the result of X ray treatment of gynæcomastia may be explained by the presence of hyperplasia of the parenchymal cells, together with hyperplasia of the periductal, loose, young, connective tissue stroma in this condition. This type of stroma is frequently seen in gynæcomastia of short duration. Irradiation seems to have a specific retarding effect on the growth of this young connective tissue element, as well as a tendency to produce atrophy of the parenchymal cells. If the hypertrophy is maintained for a longer period, the young fibrous tissue condenses and becomes more mature. X ray treatment does not seem to have any effect on the maturing or matured fibrous hyperplasia. He goes on to remark that in all probability the first treatment used in tumefaction of the male breast was rest and advice not to manipulate the part. This was the natural result of the limited knowledge of gynæcomastia that prevailed at the time. Up to the present time, the accepted treatment for gynæcomastia has been to leave it alone. If pain is not relieved by suggestion and palliative measures, and if the deformity is a constant source of mental anxiety, amputation is considered. In view of the findings recorded, X radiation should be resorted to in all cases of gynæcomastia of short duration. Best results seem to be obtained in diffuse enlargements in cases in which the young periductal fibrous tissue is in abundance. After X ray treatment has been given a fair trial, if the results are found to be unsatisfactory, a more radical procedure is to be considered.

British Medical Association News.

SCIENTIFIC.

THE ANNUAL MEETING OF THE SECTION OF OTO-RHINO-LARYNGOLOGY OF THE NEW SOUTH WALES BRANCH OF THE BRITISH MEDICAL ASSOCIATION was held at Sydney Hospital on December 8, 1931.

Election of Office-Bearers.

The following office-bearers were elected for the ensuing twelve months:

President: Dr. A. B. K. Watkins.
Vice-President: Dr. Garnet Halloran.
Honorary Secretary: Dr. Ashleigh Davy.
Honorary Treasurer: Dr. Hamilton Kirkland.
Committee: Dr. H. S. Marsh, Dr. E. P. Blashki, Dr. H. B. Harwood.
Publications Committee: The President, The Honorary Secretary, Dr. R. S. Godsall, Dr. D. G. Carruthers.

Laryngo-Fissure for Intrinsic Laryngeal Carcinoma.

DR. H. S. KIRKLAND showed a patient, aged sixty-six years, who was seen in November, 1930, complaining of hoarseness for five months. On examination the left vocal cord was thickened throughout its whole length, but there was no fixation. No glands were palpable in the neck. There was no history of syphilis or tuberculosis. There was no reaction to the Wassermann test.

By the indirect method a snipping was obtained from the cord, which on microscopical examination proved to be epitheliomatous. Laryngo-fissure was done and the cord, including the anterior end, was removed, together with a wide margin of healthy tissue.

The pathologist reported no growth in the margins of the tissue. The patient made a very good recovery and was out of hospital in ten days. His voice started to improve about one month after leaving hospital, and he recovered with a reasonably good voice. This was surprising in view of the wide gap, quite 1·5 millimetres (one-sixteenth of an inch) between the remaining healthy cord and the opposite side.

DR. G. HALLORAN asked did Dr. Kirkland remove the whole of the thyreoid ala with the cord, and how quickly did he let the man up out of bed after the operation. Did Dr. Kirkland consider Broca's classification of use in prognosis of these cases?

DR. A. DAVY asked what anæsthetic was used in this case. In three cases in his experience three different anæsthetics had been used, local, "Avertin", and intratracheally administered ether. He understood that this operation was done under chloroform. The danger of post-operative pneumonia in these cases was so great that the question of the anæsthetic was most important.

Dr. B. B. BLOMFIELD stated that when he was in Vienna two years ago, great interest was being taken in these cases and Dr. Haslinger was very definite in saying that if there was any sign of the growth around the anterior commissure, laryngo-fissure was useless and laryngectomy indicated.

DR. A. B. K. WATKINS remarked that Broder's classification depended largely on the relative amount of connective tissue to cellular tissue present in the tumour. In America it had recently been sometimes found unreliable. Dr. Watkins then questioned all members present to determine how many intrinsic laryngeal cancers had been seen. Altogether only eighteen cases had come under the personal care of those present.

Dr. Kirkland, in reply to Dr. Halloran, stated that he had left the thyreoid ala intact, and he kept the patient in bed for about four days.

In reply to Dr. Davy he stated that he agreed as to the importance of the choice of anæsthetic. He had done three of these operations. In the first one he had used ether. That particular operation was a failure, as the growth recurred very shortly afterwards, but this was not the fault of the anæsthetic used. The second was also done under ether anæsthesia and the patient developed a lung abscess, but eventually made a good recovery. In the last case chloroform was used and no trouble was experienced.

Rib Cartilage Graft After External Frontal Sinus Operation.

DR. A. B. K. WATKINS showed a patient on whom he had performed an external right frontal sinus operation for fulminating acute frontal sinusitis on September 13, 1928. The patient was suspected of already having developed frontal encephalitis. In order to save time and provide best possible drainage, no bridge had been left. On November 1, 1929, the patient was quite well, but complained of the deep depression in the region of the right eyebrow.

Through a button-hole incision above and behind the external canthus, and another longer incision above the median end of the previous incision, the soft tissues were all elevated from the bone. The skin over the scar was very thin and care was necessary. The upper end of the nasal opening into the sinus was exposed and was plugged by a pedical fat graft. A shaped rib cartilage graft was inserted and wounds closed with the result shown. If any defect had been found at the original operation in the posterior sinus wall, the graft operation would have been inadvisable.

In reply to questions Dr. Watkins stated that he would not attempt such a graft until at least six months after the first operation, and he preferred to leave it for a year. Any sign of suppuration still present in the sinus was an absolute contraindication to any attempt at grafting.

Asymmetry of Frontal Sinuses.

DR. E. P. BLASHKI showed a patient who complained of left-sided frontal pain and who, in spite of good drainage being instituted in the left frontal sinus intranasally, was not relieved. At an attempt to do Harmer's operation at the usual site on the left side, the probe came out of the right nostril. Eventually it was realized that the right frontal sinus extended far over to the left side and had been opened when it was thought the left sinus was being opened.

Harmer's operation was then performed on both sides, but through a misunderstanding on the part of the house surgeon the intubation was stopped after a few days and drainage was unsatisfactory. It appeared that a frontal osteitis was commencing, and a double radical frontal operation was performed with complete obliteration of the sinuses. It was proposed in a few days to excise the cicatrix and bring the edges of the wound together.

DR. G. HALLORAN asked whether it was not possible that there had been a congenital dehiscence in the interfrontal septum.

Dr. Watkins thanked Dr. Blashki for his very instructive case.

In reply to Dr. Halloran, Dr. Blashki stated that there was no dehiscence in the interfrontal septum.

Hodgkin's Disease.

DR. RAMSAY BEAVIS showed a boy with glands in his neck thought to be secondary to a chronic inflammatory affection of the throat. He found, however, that the glands appeared unlike the usual cervical adenitis secondary to naso-pharyngeal infections, and referred the patient to a physician, who considered it a typical case of Hodgkin's disease, although the results of tests were not yet to hand.

Nasal Speech.

Dr. Beavis also demonstrated a boy who had marked nasal speech. He had this speech before his tonsils and adenoids were removed and the operation had effected no improvement. Dr. Beavis asked whether anyone could suggest treatment to overcome this speech defect; he himself considered that it was entirely a matter of training.

DR. G. HALLORAN remembered a patient with marked nasal speech, a girl in her late teens; the cause of the

speech defect could not be explained until her condition was finally diagnosed as *myasthenia gravis*.

Dr. Watkins remarked that the only way to be sure of the diagnosis of Hodgkin's disease would be to excise one of the glands and examine it microscopically. Blood examination alone was inconclusive. As regards Dr. Beavis's second case, he asked whether any other symptoms were present pointing to *myasthenia gravis*. Patients with *myasthenia gravis* had been known to die of laughing. They laughed until they were too tired to breathe.

Dr. Beavis in reply said that he would have one of the glands from his first patient excised for examination.

No other symptoms were present in his second patient.

Tooth Plates Impacted in the Œsophagus.

DR. ASHLEIGH DAVY demonstrated two tooth plates recently recovered by him from the œsophagus, at the Royal Prince Alfred Hospital. An interesting feature of these cases was that a previous attempt had been made to remove the plates by œsophagoscopy elsewhere, where facilities for cutting these plates *in situ* were unavailable. Both plates were quite immovable with any reasonable force until they were cut across with special scissors. The first one was cut into two and the second into three pieces before the impacted portions could be removed. Both patients made uninterrupted recoveries.

The chief requirements for these cases were: (i) Deep intratracheal anæsthesia, (ii) a very wide bored œsophagoscope, (iii) special scissors. Without a deep general anæsthetic it was dangerous to pass a sufficiently large œsophagoscope to allow the forceps and scissors to be used at the same time under clear vision.

These cases clearly illustrated the fact that it was impossible to deal with some endoscopy cases without very complete equipment. No public hospital in his experience had a really adequate endoscopy set. He said that in his opinion several lives were probably lost each year in Australia through lack of complete endoscopy instrumentation.

DR. E. P. BLASHKI agreed with the remarks about the poor equipment for endoscopy at metropolitan hospitals. He considered that in every big city there should be a central depôt where these instruments could be available to all men on the staffs of the various hospitals.

After discussion the following motion was carried unanimously:

> That it is the opinion of this meeting that the metropolitan hospitals are inadequately equipped with endoscopy instruments and that the attention of the Hospitals Commission be drawn to this dangerous lack of life saving instruments.

A MEETING OF THE QUEENSLAND BRANCH OF THE BRITISH MEDICAL ASSOCIATION was held at the Brisbane Hospital, Brisbane, on March 3, 1932. The meeting took the form of a series of demonstrations by the members of the honorary staff.

Compound Fracture of the Tibia.

DR. E. S. MEYERS showed a male patient who was admitted to hospital on January 2, 1932, suffering from a severe compound fracture of the tibia. It was decided to use the method of local anæsthesia, which had given good results with simple fractures. "Novocain" was used; the needle was pushed in through the sound skin and then down until the gap between the two ends of the bone was reached. Complete anæsthesia was obtained, twenty cubic centimetres being used in all. The wound was cleaned and the limb was enclosed in plaster to a level above the knee, the plaster being reinforced with a thick slab behind the knee. The patient could now lift the leg and union seemed firm. He was having reeducation and was to wear a caliper later.

Subphrenic Abscess.

Dr. Meyers also showed a male patient whom he had treated in conjunction with Dr. A. P. Murphy. The patient had been referred to the hospital by a country practitioner, who wrote as follows:

> On October 8, 1931, operation had been performed on the patient for subacute appendicitis. For four days the patient had progressed satisfactorily; on the fifth day the temperature had risen and severe colitis had developed, the patient passing eighteen stools in eight hours. The abdomen had been distended and hard, showing a peritonitic condition. For ten days the temperature had varied from 100° to 104° F., and then pus and fæces had come through the wound. The temperature was still raised, though the discharge of fæces had practically ceased.

Dr. Meyers stated that the patient on admission had been coughing up very foul material. He had apparently had a subphrenic abscess, which had discharged through the peritoneal cavity and through the lung. He was treated with masterly inactivity. Dr. Murphy saw him frequently and Dr. Cross injected the lungs with lipiodol, X rays demonstrating the condition. The patient progressed rapidly after admission and was now so well that no treatment was indicated.

Colles Fracture.

DR. G. A. C. DOUGLAS showed a male patient, aged sixty-nine years, who had fallen from a horse two weeks previously. He had fallen on to his hand and had sustained a Colles fracture. Dr. Douglas showed the patient particularly to illustrate the position of putting up the fracture. The deformity had been reduced. The important point was that the surgeon must have due appreciation of what the deformity was. If impacted, the fracture was first disimpacted, then manipulation performed, the bones being brought into alignment and the radius into its correct position. The hand was then put into plaster. Several points were important. The hand must be in flexion; sometimes ulnar deviation was required (in this case the hand was fairly square); also the hand must be in pronation. The elbow was included in the splint; the fingers were left out for use and active movement, and the thumb and thenar eminence were left out. An essential point was that there should be movement of the fingers, even if there were pain. The extensor tendons were almost in contact with the bone, and adhesions formed before one was aware of them.

Dr. Douglas demonstrated a recent Colles fracture which had been found in a cadaver in the dissecting room.

Resection of Presacral Nerves for Vesical Pain.

DR. JOHN POWER showed a female patient, aged fifty years, who had been attending the hospital for nine years. She had been suspected of having a tuberculous bladder and had been subjected to cystoscopy by four different surgeons, but the diagnosis was not confirmed. Dr. Power had been treating her for two years with medication and local injections in every form. He had thought she was suffering from an interstitial cystitis or a Hunner's ulcer, as there was a small area above and mesial to the left ureteric orifice, which bled freely. She had had irrigations and the bladder had been distended, with no relief. Diathermy had been used with only temporary relief. Finally, she had been admitted to hospital, and her complaint was that she wanted to urinate "all the time". It was thought a cure or relief might be obtained by resecting the presacral nerves. Operation was performed. An incision was made over the inner border of the left rectus muscle, one-third above and two-thirds below the level of the umbilicus. The patient was very thin and it was easy to pack off the intestines. An incision was then made in the peritoneum over the bifurcation of the abdominal aorta. The peritoneum was cut up and down over the sacrum; it was very easy to pick up the plexus in front of the bifurcation of the aorta. Five centimetres (two inches) of the plexus were removed.

At present there was still much infection in the urinary tract. The patient was discharged with a time capacity of four hours; she had no pain, but still had some discomfort, and the capacity of her bladder was eight ounces. The patient herself was very pleased with the result, laying emphasis on the difference between discomfort and pain.

Enterogenous Cyanosis.

DR. EUSTACE RUSSELL showed a female patient suffering from cyanosis, whose condition had been very difficult to diagnose. Dr. Russell said that cyanosis might be due to many causes, from air hunger to chewing cordite. These causes could be classified as follows: (i) Endogenous causes, respiratory or cardiac. (ii) Exogenous, due to drugs such as acetanilide, sulphonal, carbon dioxide, methane, potassium chlorate *et cetera*. (iii) Enterogenous. (iv) *Polycythæmia vera*, which was a fairly rare condition.

In the respiratory group were included obstruction due to a foreign body, spasm, inflammatory conditions and tumours. The patient shown had been under observation for some ten years. A diagnosis had not been made, but it was thought that the condition was due to the too free administration of some sedative, for example, "Sitruc" powders or aspirin. Now it was found that the condition probably belonged to the enterogenous group.

The patient had complained of giddiness and weakness for two years. Twelve years previously she had had an operation performed for the removal of gall stones and she had been cyanosed ever since. Two years ago a venesection was performed, as her medical attendant at the time considered she was suffering from *polycythæmia vera*. In addition to the cyanosis, she had complained for some months of tightness in the chest, shortness of breath and vomiting attacks. She had had severe colds, and had lost one stone in weight in the last twelve months. The blood film was normal in appearance; there were 4,600,000 red cells per cubic millimetre, and 7,800 white cells. This result ruled out *polycythæmia vera*. Patients suffering from *polycythæmia vera* almost invariably showed a florid complexion and a rubicund look, and the red cell count was rarely under 7,000,000 per cubic millimetre, and frequently the number of cells was as high as 12,000,000. This patient, on the contrary, had a pinched and bluish look; her blood pressure was normal, there was no enlargement of the spleen, and there was a tendency to hæmorrhages. A test meal revealed that there was no free hydrochloric acid in the stomach. A second blood examination showed that the red cell count had risen to 5,000,000 per cubic millimetre. The diagnosis was made of enterogenous cyanosis, due to the *Bacillus nitrosi*. This bacillus had not yet been isolated, although all methods had been tried. Dr. Duhig had made a spectroscopic examination of the blood and had reported a sulphhæmoglobinæmia. The patient had been treated with Haldane's oxygen administration apparatus, to try to bring back a healthy colour to the cheeks, but the oxygen was not taken up by the blood and there was no change in colour.

Pulmonary Tumour.

Dr. Russell also showed a male patient, illustrating a respiratory cyanosis due to pressure. He had been seen for the first time two days previously, and was presumed to be suffering from a neoplasm of the mediastinum. He complained of pain in the right side of the chest, cough and hæmoptysis. He had had no breathlessness. The pain was worse at night, and the patient had lost two stone in weight in the last four months. He suffered from anorexia; the bowels were well opened. The right arm and leg swelled, but the swelling would subside quickly; puffiness under the eyes was sometimes noticed.

On examination the right side of the face was found to be puffy, the right arm was enormously swollen, the right leg was also swollen. The right external jugular vein was very prominent and there was a very pronounced swelling on the right side of the neck. The patient was very cyanosed. There was dulness all over the right side of the chest, and X ray examination revealed that the right side of the chest was completely opaque. There was no tracheal tugging or inequality of the pupils and the obstruction appeared to be purely venous. The patient's blood did not react to the Wassermann test. Aspiration of the right pleural cavity had revealed only a small quantity of fluid containing a few lymphocytes. There were no bacteria present and no blood, and the fluid was sterile on incubation. A diagnosis had been made of lymphosarcoma of the right mediastinum.

Auto-Gastro-Enterostomy.

Dr. Russell's third patient was a man who illustrated how some surgical procedures could be brought about without the intervention of the surgeon. The patient was aged fifty-two years. He had seen war service and had lost the sight of one eye. He had also suffered a spinal injury. He gave a history of having fainted four days before admission. He had passed two foul motions. After admission an enema was given with a black mass as result. The patient was severely ill for some days, and a blood transfusion was considered, but was not done. A blood count revealed a severe secondary anæmia, the red cells numbering 1,000,000 per cubic millimetre. The patient had been very difficult to feed, but he now looked and felt well. A diagnosis of peptic ulcer in the duodenum was made. X ray examination showed that the patient had "performed an auto-gastro-enterostomy". With this artificial stoma he was reasonably comfortable, taking ordinary diet and getting about well.

Oxygen Administration.

Dr. Russell then demonstrated the use of Haldane's oxygen administration apparatus.

Partial Rupture of the Capsule of the Shoulder Joint.

DR. NEVILLE SUTTON'S patient was shown by Dr. K. C. Ross. The man gave a history of having violently wrenched out his left arm four months previously, when he was lowering a bunch of bananas. He developed a large swelling along the anterior border of the axilla. This was cut down upon but not incised. The patient attended the out-patient department for six weeks. The swelling was quite translucent and movable, and a strand could be felt running up to the shoulder joint. The condition was considered to be a partial rupture of the capsule of the shoulder joint, with effusion of the synovial fluid. It was a most rare condition and probably resembled a Baker's cyst.

Bilateral Ulceration of the Tonsils.

DR. F. S. MEADE showed a male patient who had been admitted to hospital two months previously. He had complained of a sore throat for three months. On examination the tonsils were seen to be covered with a grey slough, there were excavations in them, but there was not much inflammatory reaction round them. The patient gave an indefinite history of syphilitic infection; the Wassermann test gave no reaction. Smears from the tonsils were then examined for Vincent's bacillus; the first smear gave a negative result, but in the second smear the organisms were present. Treatment was given by injections of "Neo-Salvarsan", four milligrammes being given at intervals of five days. In spite of treatment the ulceration proceeded and a large portion of each tonsil was ulcerated away. The condition then spread down the lateral wall of the pharynx and there was thickening of the epiglottis and arytenoids. It was at first thought that Vincent's infection would not extend below the pillars of the fauces, but it was now known that it did extend so far and had even gone down to the parenchyma of the lung. The patient was now responding to treatment.

Pulmonary Fibrosis with Cyanosis.

DR. D. A. A. DAVIS showed a man, aged twenty-six years, who was complaining of cyanosis and dyspnœa. He was born in Leicester and had left England eight years ago. He had influenza in England in 1917. There was nothing of importance in the family history. The patient stated that he had first noticed his blue colour in February, 1928, when he had an attack of bronchitis which lasted for ten days. In April, 1928, he had another attack of bronchitis, again lasting for ten days. The patient stated that in each instance the cyanosis had disappeared at the end of the attack. In March, 1929, and March, 1930, he suffered from similar attacks. When he was discharged from the Maleny Hospital in March, 1930, he noticed that the cyanosis persisted, although the wheezing left him. He first noticed persistent dyspnœa early in 1931, and he was admitted to the Brisbane Hospital in May, 1931, com-

plaining of dyspnœa, cough, slight swelling of the feet at night, and some loss of weight.

On examination the physical signs in the chest were those of emphysema; the heart sounds revealed no abnormality and the blood pressure was normal. A blood count at this time revealed over 6,000,000 red cells per cubic millimetre; spectroscopic examination of the blood failed to reveal any abnormal bands. X ray examination of the chest showed increase of hilar markings with calcifications. The apices and bases of the lungs were clear. An X ray screening of the heart failed to reveal any definite cardiac enlargement. The patient's chest expansion diminished from 6·25 centimetres (two and a half inches) in May, 1931, to less than five centimetres (two inches) at the present time. In January, 1932, the blood count revealed 4,500,000 million red cells per cubic millimetre. A spectroscopic examination again failed to reveal an abnormality. In June, 1931, and in September, 1931, the Wassermann test yielded a positive reaction ("++++"). In January, 1932, following on a course of "Bismol", the Wassermann reaction was still positive ("+++"). The Lewis test gave the results 84:150:78. Renal function had been unsatisfactory throughout. The patient left hospital for a few weeks in November, 1931, and undertook milking, but he found it made him too dyspnœic, and he reentered hospital.

Dr. Davis read the following extracts from a description of Ayerza's disease:

> This is a disease and dilatation of the pulmonary arteries, in most cases of syphilitic origin. The arterioles become surrounded and blocked, with consequent dilatation of the right heart. The disease develops insidiously with two main symptoms, dyspnœa and cyanosis; the dyspnœa usually appears before the cyanosis. X rays show a distinct dilatation of the pulmonary artery, seen just below the knuckle of the aorta on the left side. Electrocardiogram shows right ventricular predominance. There are no constant physical signs in the lungs, although emphysema and œdema may be found.

This case differed from the typical case in that the cyanosis appeared to have developed coincidently with the dyspnœa. Also the X ray findings had not borne out the diagnosis of Ayerza's disease.

Supposed Addison's Disease.

DR. CYRIL SHELLSHEAR showed a female patient who was four months pregnant and who had been sent into hospital for an induction of labour, as she was supposed to be suffering from Addison's disease. The gynæcologist who had seen her on admission was not satisfied with the diagnosis, and had her transferred to the care of the physicians. The patient complained of a pigmentation of her skin, commencing ten months before, which was rapidly increasing. A glucose tolerance test was performed and yielded a figure of 0·78%.

The urine contained bile. The Wassermann test yielded a positive result. The systolic blood pressure was 112 and the diastolic pressure 60 millimetres of mercury. There was no enlargement of the liver and there was no intrabuccal pigmentation, such as usually occurred in Addison's disease.

Aortic Aneurysm.

DR. ALEX MURPHY showed a male patient, aged fifty-two years, who was admitted to the hospital in January, 1931, complaining of a pain in the upper part of the chest of three months' duration. He was not breathless on exertion; the pain came on mostly in the evening and he suffered from palpitation. He had lost two stone in weight in the last year. He was a married man; his wife had seven children and had had one miscarriage. The husband said she had been an invalid for several years on account of heart trouble. On examination, there was dulness on percussion to the right and left of the sternum; there was visible pulsation in the second and third interspaces. There was a two-and-fro aortic murmur over the tumour. The pulse in the left arm was found to be smaller than that in the right, and there was half a cardiac cycle between the two. This difference in timing and volume was obvious. The systolic blood pressure in the right arm was 126 and the diastolic pressure 64 millimetres of mercury, whereas in the left arm the systolic pressure was 97 and the diastolic pressure 78 millimetres of mercury. The Wassermann test gave a strongly positive reaction.

Avulsion of the Phrenic Nerve.

DR. ALEX MURPHY and DR. E. S. MEYERS showed a male patient who was admitted in December, 1931, suffering from unilateral pulmonary tuberculosis. The patient had complained of cough and the presence of sputum for four months. He was very easily tired and was losing weight. He gave a history of having had pleurisy four years previously. X ray examination showed that fibrosis was present and that the mediastinum was drawn over to the affected side. Dr. Meyers performed the operation of avulsion of the phrenic nerve on that side. The patient was febrile before operation, the temperature varying from 37·3° to 37·8° C. (99·2° to 100° F.) and over. Four days after the operation the temperature fell to normal; within fourteen days the cough disappeared and there was no sputum. The patient gained 2·2 kilograms (five pounds) in weight. X ray examination showed the rise in the level of the diaphragm since the operation. Dr. Murphy stated that the rise in the height of the diaphragm would probably increase still more in the next twelve months.

Sequestrum of the Radius.

DR. HAROLD CRAWFORD showed a male patient, aged seventeen years. He was admitted on December 21, 1931, from the Gympie Hospital, with a history that five weeks previously he had been thrown from a motor truck and had sustained a compound fracture of the lower end of the right radius and ulna. The wound was treated by drainage *et cetera*. Two weeks after the accident there was severe hæmorrhage from the wound; since then there had been four such hæmorrhages, and a severe one occurred on the morning of admission. At that time the wound was cleaned and packed with vaseline gauze. On December 27, 1931, there was a recurrence of hæmorrhage. The swelling round the injury subsided and there was found to be a traumatic aneurysm of the radial artery. Under local anæsthesia the artery was tied proximal and distal to the aneurysm and the wound packed with vaseline gauze. On February 5, 1932, the lower end of the shaft of the humerus was removed as a sequestrum. It was free and was removed without difficulty.

Dr. Crawford said that this case was of interest on account of several features, namely, the formation of a traumatic aneurysm of the radial artery, the massive sequestration of the lower end of the radius followed by rapid reformation of the shaft from the periosteum, with good functional result, and the possibility of subsequent deformity due to interference with the epiphyses of the lower end of the radius which did not unite till the twenty-first to the twenty-fifth year.

Transverse Myelitis.

DR. JOHN BOSTOCK showed a male patient, who gave a history that one night in October, 1931, he had gone to bed quite well. About midnight he got out of bed to see to his children and was quite well. At 3 a.m. he awoke and found that he could not turn in bed. There was complete inability to move or to feel the lower limbs. He was admitted to hospital, and on examination was found to have complete paralysis of both lower limbs and, below the twelfth dorsal nerve, complete insensibility to every form of stimulus. There was retention of urine. A Wassermann test was performed on the cerebro-spinal fluid and on the blood, and in each case the result was strongly positive ("++++"). A diagnosis was made of syphilitic myelitis. Antisyphilitic treatment was carried out with mercury and potassium iodide and with injections of "Neo-Kharsivan" and "Bismol". Treatment with malarial infection was also carried out and a very good reaction obtained. At the present time the patient could move both legs, could feel in both legs, and could coordinate remarkably well. There were some residual signs still

present. Marked clonus was present and there the plantar reflexes were extensor in type, though this was less pronounced. With regard to sensation, the vibration sense was normal and there was some thermal sense, though this was slightly inaccurate. Above the level of the twelfth dorsal nerve sensation was quite normal. The patient could get about a little and was regaining control of his bladder. Dr. Power had seen the patient and had advised that an indwelling catheter be left in for some weeks, being removed every three days to see whether there were any control over the bladder. The condition had gradually improved and now the patient only got incontinence after any hurried movement.

Dr. Bostock said the condition was evidently the result of a thrombosis of an artery in the cord, probably the anterior spinal artery, with subsequent surrounding œdema, which completely disorganized the cord.

Ventriculogram.

DR. JOHN BOSTOCK and DR. A. G. ANDERSON reported the history of a male patient who was admitted on January 29, 1932, and on whom a ventriculogram had been performed. The patient had complained of severe headache for the last nine months; his eyesight had been failing rapidly and he had had vomiting attacks for two months. He suffered from frequent micturition and had had incontinence for the last two months. The patient was found to be dull mentally, he was giddy and walked with a disordered gait. Ophthalmoscopic examination revealed five diopters of papilledema. A diagnosis was made of an intra- or supratentorial lesion. Dr. Anderson prepared a ventriculogram, which revealed an intratentorial lesion. The patient subsequently died and a *post mortem* examination revealed a tumour in the cerebellum.

Dr. Anderson said he had followed the method of Fraser in admitting air into the ventricles. Two points were taken, six centimetres above the external occipital protuberance and three centimetres either side of the mid-line. Under local anæsthesia with "Eucaine" a trephine with a small burr was used to penetrate the skull at these two points. Needles were passed through these openings parallel to each other, to a depth of four to five centimetres. They struck the ventricle in its supero-posterior aspect. If there were any increased intracranial pressure the needles were allowed to drip, then a small quantity, probably about ten cubic centimetres, of cerebro-spinal fluid was very slowly extracted from each ventricle. Into the right ventricle one cubic centimetre of indigo-carmine was then injected. After five minutes' interval it was found that indigo-carmine could be extracted from both cannulæ, showing that the foramen of Munro was patent and that there was a definite communication between the lateral ventricles. X ray photographs were then taken, and these demonstrated definite bulging of the posterior horn in both lateral pictures.

A MEETING OF THE SOUTH AUSTRALIAN BRANCH OF THE BRITISH MEDICAL ASSOCIATION was held at the Children's Hospital, Adelaide, on March 31, 1932, DR. A. BENSON, the President, in the chair. The meeting took the form of a series of clinical demonstrations.

Abscess of the Lung.

DR. E. BRITTEN JONES showed a boy, aged seven years, suffering from an abscess of the lung. Twenty-two days after an operation for removal of tonsils he expectorated about two ounces of pus.

The abscess was situated in the inferior lobe of the right lung. The pus expectorated contained a fusiform bacillus; in view of this, a course of treatment with "Myosalvarsan" was undertaken. At the end of five weeks' treatment the patient was free from signs and symptoms, and radiological examination disclosed a corresponding improvement. Dr. Britten Jones did not think it justifiable to attribute the satisfactory result entirely to the "Myosalvarsan".

Hydronephrosis.

DR. E. F. WEST showed the specimens from two cases of bilateral congenital hydronephrosis in the new-born.

The first case was that of a male child, aged two weeks. The pelves of both kidneys were dilated to over three times the normal size. The calyces were dilated. The kidneys were much enlarged. The ureters were both dilated to a diameter of approximately one centimetre and were very convoluted. The dilatation of the ureters extended to the bladder wall. Ureteric orifices were tightly contracted and admitted a very small probe with difficulty. The bladder wall was thickened and showed evidence of hæmorrhagic cystitis. The urethra, when slit up, showed no stricture, valve of the *verumontanum*, or other obstruction. Obstruction in this instance, if any, was considered to be at the ureteric orifices.

The second case was that of a male child, aged three weeks. The renal pelves, calyces and ureters were dilated as in the first case. The kidneys were very enlarged, with multiple small abscesses scattered throughout their substance.

Hare Lip and Cleft Palate.

DR. C. DUGUID showed a boy of six years on whom he had operated for double hare lip and cleft palate. On the right side the lip was split up to the nostril; on the left side the cleft was complete. The premaxilla protruded from under the nose with torsion to the right. There was marked flattening of the left nostril. The soft palate was unaffected. The hard palate had a wide V-shaped gap, which was operated on at three months after the manner of Brophy. The hare lip and left nostril were operated on at six months.

The result was attributed to elimination of tension. The cheek on both sides and the left *ala nasi* were completely separated from the bone by a periosteal elevator. The muscle layer of lip flaps was separated by a very sharp knife from the skin and mucous membrane, and the strain of coaptation was taken by the muscle layer. There was no tension when stitching the skin edges and the edges of the mucous membrane.

The father and a paternal uncle had cleft palate and hare lip, and in the same family as the paternal grandmother there was a child born with a cleft condition of the face incompatible with life.

Acute Aseptic Meningitis.

DR. M. T. COCKBURN showed a boy, aged three years and six months, who had been perfectly well until three days previous to March 1, when he suddenly complained of pain in the head and stomach followed by screaming and vomiting. After several hours' drowsiness he apparently recovered. The following day there was a recurrence of symptoms followed by the same apparent recovery. At midnight that night he woke up screaming, and vomited, and it was noticed that his neck had become stiff. There was no history of previous illness, and the family history was clear. The important features of the clinical examination were: a temperature of 38·9° C. (102° F.), a pulse rate of 130, and a respiration rate of 32. The boy lay on his left side, was drowsy and irritable. There was extreme retraction of the head, with stiffness of the neck. There was some slight injection of the left *membrana tympani*. There was no muscular weakness detected and the *fundus oculi* was normal. There was a bilateral positive Kernig's sign, absence of deep reflexes and normal plantar response. Twenty cubic centimetres of anti-meningococcal serum were given intramuscularly and repeated the next day. The boy's condition became worse for the first four days, and a paralysis of the left sixth cranial nerve developed. Lumbar puncture was repeated daily for eleven days. On each occasion the fluid was under increased pressure, as measured by an attached manometer, and frankly purulent. After the eleventh day the fluid became more clear and the boy became better, the signs and symptoms disappearing completely, and the boy was discharged apparently quite well one month after admission. The cerebro-spinal fluid was reported on each occasion to contain many polymorphonuclear cells, but no organisms were obtained on culture. There was some increase in globulin, sugar was

absent, and chlorides equalled 690 milligrammes per 100 cubic centimetres. The condition was considered to be one of so-called acute aseptic meningitis.

Ankylosis of the Right Elbow Joint.

DR. IAN HAMILTON showed a male patient, aged fifty-four years, who had gonorrhœa over two years ago; this became chronic. About two years ago he developed gonorrhœal arthritis of the right shoulder, elbow and wrist joints and the small joints of the right hand and fingers. These joints gradually improved and appeared to be quiescent about eighteen months ago and had been ever since. Since then he had been treated with light, radiant heat, massage and diathermy, and on one occasion, in September, 1931, forcible manipulation of the elbow was performed.

Dr. Hamilton pointed out that the patient was a healthy man and his chronic gonorrhœa was apparently cured. The right shoulder and wrist joint functioned very well, and in all probability, judging by the wrist, the inferior radio-ulnar joint was free. The small joints of the hand and fingers had some stiffness and slight wasting of the interossei muscles, but on the whole a good 50% function of the hand was present.

The right elbow was ankylosed in a position of about 120° of flexion, half way between full pronation and supination. There was about 10° of flexion and extension present, and no pain on attempting to force the joint. There was complete ankylosis of the superior radio-ulnar joint. No signs of activity of the arthritis could be detected.

Dr. Hamilton said that this was a case of characteristic false ankylosis due to a gonococcal affection of the periarticular type. The infection was also polyarticular. In a labouring man an ankylosed elbow joint in this position was of little use. It would be better if it were ankylosed at about 45° of flexion or, better still, if a new false joint could be provided. He suggested to the meeting that in his opinion excision of the elbow joint should be performed, plenty of bone being removed and movements being started on a special splint from almost the first day. The bones would be very soft and atrophic, and the movements would help to stimulate a good new bone formation which would be more likely to give a pseudarthrosis with no lateral mobility. The result would greatly improve the patient's condition.

DR. L. O. BETTS agreed with Dr. Hamilton upon the treatment suggested, but on a point of technique said that in his opinion a better result would be obtained by immobilizing the joint for an extended period after the excision. He thought that too much new bone would be thrown out under the stimulus of early movement.

Myositis Ossificans.

DR. ALLAN LENDON showed a skiagram taken in a case of traumatic *myositis ossificans*. The patient was a male, aged forty, who had been thrown from a horse twelve months previously, sustaining severe injuries; he was unconscious for six months following the accident. He came to the out-patient department of the Adelaide Hospital complaining of a stiff left elbow since the accident. Examination showed the elbow to be absolutely immobile in extension, although almost full pronation and supination were possible. There was a bony mass palpable in the situation of the *brachialis anticus* muscle. The skiagram showed a dense bar of bone extending from the shaft of the humerus to the coronoid process of the ulna. When this bar of bone was removed at operation, the full range of movement was at once possible. Dr. Lendon was indebted to Dr. C. T. Turner for the films.

Neoplasm of the Ilium.

Dr. Lendon also showed a skiagram of a neoplasm (probably a sarcoma) of the ilium. The patient was a female, aged sixty-nine, who first consulted a doctor in October, 1931, on account of left-sided sciatica and uterine prolapse. No cause being found for the sciatica, the prolapse was operated on, and fifty cubic centimetres of saline solution were injected into the sacral canal. This procedure relieved her sciatic pain, but she still had some pain in the left buttock, and two months ago a swelling was noticed in that situation. A Casoni test was done and gave no reaction, and aspiration of the swelling yielded bright blood. When Dr. Lendon saw her, there was a rounded swelling about the size of a coconut in the region of the left sacro-iliac joint, with a somewhat irregular surface. Its consistency varied, being in parts almost fluctuant. There was no "egg shell" crackling detectable, nor any pulsation. The skiagram showed extensive destruction of the ilium and sacrum and intervening joint, with complete absence of bony reaction.

Correspondence.

UNLICENSED PRACTITIONERS.

SIR: May I be permitted to use some of your valuable space in an endeavour to arouse interest in a matter of vital importance, not only to the medical profession, but to the community in general. The subject is, I am sure, an old one; but my interest was reawakened in it by a portion of the presidential address delivered by the President of the Branch, Dr. A. J. Gibson, at the annual meeting on March 31 and published in the journal of today's date.

In stating the aims of the Association he points out, among the other objects, that it is the aim of the Association "to protect its members and the community from the dangerous and evil practices of ignorant and unscrupulous practitioners".

One immediately wonders whether Dr. Gibson is referring to medical or illegal practitioners. One takes it that he is alluding to the latter; since through the Medical Board of the State and the Ethics Committee of the Branch the erring medical practitioner is easily and readily brought to order; but, except for a rather ineffective legal statute, no control is exercised over the illegal practitioner. The activities of this kind of gentleman are all too prevalent. In the district where I am practising we are subjected to repeated visits of some of them, while others are constantly practising in the town. In all there are six, excluding a Chinese herbalist. Four of these advertise extensively in the local paper, a publication with a very wide circulation. One even inserts a half page advertisement for several days prior to his visit. This particular gentleman, who has a very widespread practice, covering a very large area of New South Wales, is reputed on an extremely reliable authority to have taken as much as four hundred pounds out of the town as the result of ten days' business.

These practitioners, too often ignorant men with no medical knowledge, frequently do considerable damage to the health of the misguided members of the general public who are foolish enough to consult them, and even in some cases endanger lives by delaying the patient from seeking reliable medical treatment. This, apart from the fact that they defraud the public of large sums of money, calls for some action on the part of the Association with the object of protecting its members and the general public.

Most practitioners to whom I have spoken on this subject appear to consider masterly inactivity the best treatment. This, however, is neither a worthy nor an expedient line of conduct for an enlightened body of men. Indeed, the opposition, nay, even derision, that one experiences whenever this subject is broached, has decided me to adopt for the present at least a *nom de plume*.

Without presuming to dictate to the Council of the Branch, they might consider some action on this matter. This might for a beginning be modelled along the lines of the *Veterinary Surgeons' Act* passed by the last Bavin Government. This Act prevents men from advertising and practising as veterinary surgeons unless qualified as such. The Act imposes a salutary punishment for breaches of the Act. Surely, then, if dumb animals are worthy of such protection, why cannot even an equal measure of protection be afforded the more valuable human lives? Large sums of money are expended every year in school medical examinations, food inspections, other public health activities, and exhibitions in medicine at the University, so, in order to be consistent, a measure to suppress these unqualified and unscrupulous practitioners should be

passed. In accordance with aim number six, as set forth in the President's address, it would be quite within the scope of the Association to induce the Government of the State to place such a measure on the Statute Book.

Apologizing for occupying so much of your space.

Yours, etc.,

"MEDICUS."

April 23, 1932.

THE LATE JOHN EDGAR WOLFHAGEN.

SIR: In the obituary notice of my old friend in the journal of April 23 it is stated that he graduated in 1883. This is an error. He and I went through the course together and graduated in 1884. He belonged to a small "set" within a set of Australians of whom the only survivors now are Dr. Davenport, of St. Kilda, Dr. Challinor Purchas, of Auckland, Dr. Chisholm Ross and Dr. T. H. Barker, of Sydney, and myself. He had a most genial, companionable personality, and was a most assiduous, conscientious worker.

Yours, etc.,

F. ANTILL POCKLEY.

Wahroonga,
New South Wales,
April 27, 1932.

ACCOMMODATION IN MONOTREMES AND MARSUPIALS.

SIR: Dr. Becket rightly draws attention to the dominance of smell and hearing and the relatively defective vision of dogs, also to the dominance of vision in birds and in the primates. The riddle is, however, that some half dozen different methods of accommodation exist apparently in a capricious manner in animals.

Furthermore, in the mammals, the mechanism often remains in a form which is rudimentary and practically useless. Why is it retained, and why does it reappear? What is it that causes different senses to become dominant whilst that of vision becomes rudimentary, but sometimes still just existant so far as accommodation is concerned? To me the whole business is quite beyond human explanation at present. I fancy the same mystery clouds many other functions and structures. The screen which shuts off any intelligible explanation is so dense that even conjecture is out of the question. Evolution with extraordinary and erratic variations there has been, but the why and wherefore is the puzzle.

Yours, etc.,

JAMES W. BARRETT.

Melbourne,
May 2, 1932.

A WARNING.

SIR: Several months ago a man presenting a card stating that he did chromium plating, instrument repairs and sharpening, visited most of the members of the Illawarra Suburbs Medical Association. His card further stated that he had been employed for eight years by Allen and Hanburys. Most of us gave him some instruments, but did not get a receipt for same from him, and when same were returned, a written-out receipt for same, duly signed and stamped, was presented, but no account.

Practically every one of us lost some expensive instrument, and as a parting shot a first-class instrument was offered at a ridiculous price to the unsuspecting. In addition to the actual loss of instruments, the chromium plating was atrociously done and many good instruments were spoiled. One of our members has taken out a warrant for the man's arrest, but up to date he cannot be found. Perhaps he has left for some other State.

Yours, etc.,

W. F. SIMMONS.

Bexley,
May 2, 1932.

HODGKIN'S DISEASE.

SIR: In THE MEDICAL JOURNAL OF AUSTRALIA (April 16, 1932) Drs. Utz and Keatinge advocate a new and distinctly bizarre method of treatment for Hodgkin's disease, and their claims are unanimously supported by the Cancer Research Treatment Subcommittee of Saint Vincent's Hospital, Sydney. On analysis of their results, however, certain features emerge which demand comment.

Duration of Observation.—It is known that the duration of untreated Hodgkin's disease may extend to five years or even longer. Utz and Keatinge's protocols indicate that their cases were under observation for an average period of only four and a half months from the commencement of treatment by chicken serum. Only seven of the twenty-six patients were under observation for at least six months from the start of the treatment, and of these only three were observed for at least one year. The maximum period of observation from the commencement of treatment was twenty-seven months (Case I).

Drs. Utz and Keatinge lay it down in the body of their paper that patients "cannot be classified as cured until several years elapse after the cessation of all treatment". Nevertheless, the Treatment Subcommittee of Saint Vincent's Hospital claims two cures, though no single case had remained well even for one year after the cessation of treatment. The "astoundingly successful" Case I was only observed for three months after treatment ceased.

The Influence of Auxiliary Methods of Treatment.—In 19 of the 26 cases X radiation was used therapeutically along with or just prior to the injections of fowl serum. It has been known for many years that X ray therapy frequently produces temporary disappearance of the lesions of Hodgkin's disease and that the disease may be controlled and life prolonged for many years by use of this agent. Indeed, several of Utz and Keatinge's cases strikingly exemplify this. Thus the duration of Case XIV under repeated X ray treatment, and prior to the administration of chick serum, was thirteen years; Case XVIII had X ray therapy for seven years, and was then apparently well, with no glands palpable, before serum was employed; and in Case XXIV, with a duration of two years, no serum was used at any time; but, as the result of X radiation, all enlarged glands completely disappeared. The protocol of Case I, in which the Research Subcommittee regarded the serum treatment as "an unqualified and really astounding success", deserves comment regarding the influence of the X ray therapy employed. After combined X ray and serum treatment from June to October, 1929, there were "no glands palpable in any area". In January, 1930, further cervical glandular enlargement appeared. A long course of serum treatment from March to July, 1930, is stated to have been accompanied by some diminution of these glands, but in September the "glands appeared stationary". In September and October repeated X ray treatment was given, and at the end of October the glands had "completely disappeared". In March, 1931, abdominal glandular enlargement was detected, and after repeated X radiation and three doses of chicken serum, it is noted in May, 1931, that these glands had disappeared. In this case, then, it is evident that following X rays alone or X rays *plus* serum, enlarged glands disappeared, but that this happy result did not ensue upon a long course of serum alone.

A final point regarding the X radiation of Utz and Keatinge's cases may be noted. Of the five fatal cases recorded (II, III, VIII, X and XII), three were treated by serum only without simultaneous X radiation (II, X and XII).

Case VII merits special mention; for : (i) it was treated by the authors with serum only, and (ii) it was observed for nine months after the cessation of treatment without its showing signs of recurrence. This patient, however, had been for one year to eighteen months in the Royal Prince Alfred Hospital with enlarged glands in the groin and neck, and we are not informed by the authors what X ray or other treatment was used during this time. More detail about the treatment of this case is desirable.

The Technique of the Production and Use of Serum.—Utz and Keatinge state that never in any instance has serum been used if a period of three days has elapsed since withdrawal from the hen. Yet, in giving their

method of serum preparation and use they describe a sterility test of the serum followed by a toxicity test in the guinea-pig, and the next day the administration of the first dose of serum to the patient, two days later a second dose being given. It is difficult to see how the second dose could be given within the three days, even if only one day each were allowed for the sterility and toxicity tests of the serum.

The authors found by experimentation that the hen was ready for bleeding twelve days after inoculation, but the nature of the experimentation is not disclosed. This matter is of great importance and should be fully elaborated by the authors.

The Diagnosis.—Utz and Keatinge's paper does not adequately demonstrate the accuracy of the diagnosis in many of the cases described. The clinical details are meagre; the Wassermann reaction is recorded in only one case, and only one of the fatal cases came to autopsy. The diagnosis was not established histologically in Cases IX, XII, XV, XVII, XVIII and XXIII, and was admittedly doubtful in Cases XXI, XXII and XXV. In the remaining cases the diagnosis of Hodgkin's disease is stated to have been made histologically, but no complete accounts and no photographs of the microscopical appearances observed are given.

The histological diagnosis of Hodgkin's disease is sometimes by no means an easy matter, and workers who, like one of us (R.W.), have experienced difficulty in this respect, will require a more adequate description of the lesions before fully accepting the diagnosis in all of these cases.

However, in our opinion, it is not the accuracy of diagnosis which is most open to criticism in Utz and Keatinge's paper. Even if all of their cases be accepted as undoubted Hodgkin's disease, the exceedingly brief average period of observation following treatment and the failure to assess the great therapeutic value of X radiation employed in most of their cases render it impossible to draw any valid conclusions regarding the efficacy or otherwise of chicken serum therapy.

Yours, etc.,

WILLIAM JAS. PENFOLD, M.B., B.Hy.,
Director of the Baker Research Institute.

RUPERT A. WILLIS, M.D., D.Sc.,
Pathologist, Alfred Hospital.

Alfred Hospital,
Melbourne,
May 5, 1932.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.

SIR: I have just received a cablegram about the forthcoming election to the Council of the Royal College of Surgeons of England. This contains some important confidential information, and as it is essential that all Fellows should know this before returning their ballot papers, I would request them to communicate with me before voting.

Yours, etc.,

M. P. SUSMAN.

141, Macquarie Street,
Sydney,
May 13, 1932.

STAMMERING, A NATIONAL TRAGEDY.

SIR: In reply to Dr. Leary's very excellent paper (*vide* THE MEDICAL JOURNAL OF AUSTRALIA, March 12, 1932). Few medical men take an interest in speech defects, and all are asked to give their opinions about the future of the stuttering child. I am pleased to congratulate him on his theory, but at the same time consider that the treatment should not be based mostly on such a theory, when one realizes that the area for speech has not yet been defined. It was at one time considered to be limited to Broca's area, but its cortical origin (by experiment) has been found to cover a much larger and unlimited area.

The gathering of impulses for speech in the cortical area, only to be interrupted by a supposed nervous state due to an inherent inferiority complex, cannot be proved. But the irregular action of the lower thoracic, diaphragmatic and abdominal muscles, can be detected by experiment and X ray findings. Stammering should not be considered "a symptom only of a speech defect, but a psychic defect externalized in speech", as he stated. Air is the fuel for speech and song; so the varied lung capacity and muscular discontrol combined with irregular laryngeal coordination should occupy a large part in the search for the causes of stuttering. Abnormal physical conditions throughout the respiratory tract of the patient must be considered. The best public speakers, orators, elocutionists and singers of note all have perfect muscular control and laryngeal and oral coordination. Long sentences and vocal gymnastics, as in the opera "Lucia", can only be indulged in by those with perfect lung capacity and respiratory control. Stutterers, it must be agreed, are on an average as physically fit and mentally alert as those without speech defects. It is difficult to say which factor comes first, the nervous element or the physical incoordination.

In conclusion, I would state that if there is no reason to believe that a "nervous element" exists, then measures should be taken to increase the air capacity by the corrrection of all nasal, oral, pharyngeal, laryngeal and thoracic complaints; and to secure rhythmical breathing by perfect muscular control, combined with laryngeal and oral coordination.

In criticism of the paragraph (page 357) which states that stammering "is the cause of psychic maladjustment, and not psychic maladjustment the underlying cause of stammering". Does Dr. Leary mean that stammering is the cause of the nervous state that brings about the inferiority complex or that the physical defect in incorrect breathing comes first?

Yours, etc.,

JAMES J. WOODBURN.

185, Macquarie Street,
Sydney.
Undated.

Obituary.

GEORGE COMYN.

WE regret to announce the death of Dr. George Comyn, which occurred on April 29, 1932, at Brisbane, Queensland.

Proceedings of the Australian Medical Boards.

VICTORIA.

THE undermentioned have been registered pursuant to the provisions of the *Medical Act*, 1928, of Victoria, as duly qualified medical practitioners:

Charlton, Robin Brett, M.B., B.S., 1931 (Univ. Melbourne), Alfred Hospital, Prahran, S.1.

Cohen, Cecil, M.B., B.S., 1931 (Univ. Melbourne), Alfred Hospital, Prahran, S.1.

Young, Sylvia Mary, M.B., B.S., 1931 (Univ. Melbourne), 233, Alma Road, East St. Kilda, S.2.

Hustler, Harry Fenwick, M.B., B.S., 1929 (Univ. Melbourne), c.o. A. E. Hustler, Esq., Seacliff, South Australia.

Moreland, John Griffiths, M.B., B.S., 1926 (Univ. Adelaide), 183, Moreland Road, Coburg.

Thomas, Philip Cedric, M.B., B.S., 1931 (Univ. Melbourne), Farnly Street, Mt. Lawley, Perth, Western Australia.

Additional diplomas registered:

Brown, Charles James Officer, F.R.C.S., 1924 (England).

Harrington, Norrie Nelson, M.D., 1931 (Univ. Melbourne).

Books Received.

COSMOLOGY, THE NEXT ESSENTIAL DOCTRINE IN HUMAN KNOWLEDGE, by Frank Trinca, M.C., M.B., B.S., Section I; 1932. Melbourne: Robertson and Mullens. Crown 4to., pp. 49, with illustrations.

THE DESERT COLUMN: LEAVES FROM THE DIARY OF AN AUSTRALIAN TROOPER IN GALLIPOLI, SINAI AND PALESTINE, by I. L. Idriess, with foreword by General Sir Harry Chauvel; 1932. Australia: Angus and Robertson Limited. Crown 8vo., pp. 387. Price: 6s. net.

WHEELER AND JACK'S HANDPOOK OF MEDICINE, revised by John Henderson, M.D., F.R.F.P.S.; Ninth Edition; 1932. Edinburgh: E. and S. Livingstone. Crown 8vo., pp. 673, with illustrations. Price: 12s. 6d. net.

DISEASES OF THE KIDNEY, by W. G. Ball, F.R.C.S., and G. Evans, M.D., F.R.C.P.; 1932. London: J. and A. Churchill. Royal 8vo., pp. 432, with eight coloured plates and 159 text figures. Price: 36s. net.

AIDS TO SURGICAL DIAGNOSIS, by C. P. G. Wakeley, F.R.C.S., F.R.S.; Second Edition; 1932. London: Baillière, Tindall and Cox. Foolscap 8vo., pp. 172. Price: 3s. 6d. net.

Diary for the Month.

MAY 24.—New South Wales Branch, B.M.A.: Medical Politics Committee.
MAY 25.—Victorian Branch, B.M.A.: Council.
MAY 26.—South Australian Branch, B.M.A.: Branch.
MAY 26.—New South Wales Branch, B.M.A.: Branch.
JUNE 1.—Western Australian Branch, B.M.A.: Council.
JUNE 1.—Victorian Branch, B.M.A.: Council.
JUNE 2.—South Australian Branch, B.M.A.: Council.
JUNE 6.—New South Wales Branch, B.M.A.: Organization and Science Committee.
JUNE 9.—New South Wales Branch, B.M.A.: Clinical Meeting.
JUNE 10.—Queensland Branch, B.M.A.: Council.
JUNE 14.—New South Wales Branch, B.M.A.: Ethics Committee.
JUNE 15.—Western Australian Branch, B.M.A.: Branch.
JUNE 21.—New South Wales Branch, B.M.A.: Executive and Finance Committee.

Medical Appointments.

Dr. F. W. Fraser (B.M.A.) has been appointed Government Medical Officer at Emmaville, New South Wales.

* * *

Dr. W. E. M. Blamey has been appointed Government Medical Officer at Quandialla, New South Wales.

* * *

Dr. A. E. Machin (B.M.A.) has been appointed a member of the Board to Control the Campaign against Tuberculosis in New South Wales.

* * *

Dr. W. J. Duck has been appointed Acting Medical Officer of Health for the Municipality of Longford, Tasmania.

* * *

Dr. W. Summons (B.M.A.) and Professor H. A. Woodruff (B.M.A.) have been appointed members of the Commission of Public Health under powers in that behalf conferred by Section 8 of the *Health Act*, 1928, Victoria, for a term of three years from March 24, 1932.

* * *

Dr. A. J. W. Philpott (B.M.A.) has been appointed to be a member of the Indeterminate Sentences Board, pursuant to the provisions of Section 531 of the *Crimes Act*, 1928, Victoria, and also to be an Inspector of Anatomy, pursuant to the provisions of Section 21 of the *Medical Act*, 1928, Victoria.

Medical Appointments Vacant, etc.

FOR announcements of medical appointments vacant, assistants, *locum tenentes* sought, etc., see "Advertiser," page xvi.

LAUNCESTON PUBLIC HOSPITAL, TASMANIA: Resident Medical Officer (male).
ROYAL AIR FORCE: Medical Officers.
THE UNIVERSITY OF SYDNEY, NEW SOUTH WALES: Lecturer in Medical Jurisprudence, Lecturer in Medical Ethics.

Medical Appointments: Important Notice.

MEDICAL practitioners are requested not to apply for any appointment referred to in the following table, without having first communicated with the Honorary Secretary of the Branch named in the first column, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

BRANCH.	APPOINTMENTS.
NEW SOUTH WALES: Honorary Secretary, 135, Macquarie Street, Sydney.	Australian Natives' Association. Ashfield and District United Friendly Societies' Dispensary. Balmain United Friendly Societies' Dispensary. Friendly Society Lodges at Casino. Leichhardt and Petersham United Friendly Societies' Dispensary. Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney. North Sydney Friendly Societies' Dispensary Limited. People's Prudential Assurance Company Limited. Phœnix Mutual Provident Society.
VICTORIAN: Honorary Secretary, Medical Society Hall, East Melbourne.	All Institutes or Medical Dispensaries. Australian Prudential Association, Proprietary, Limited. Mutual National Provident Club. National Provident Association. Hospital or other appointments outside Victoria.
QUEENSLAND: Honorary Secretary, B.M.A. Building, Adelaide Street, Brisbane.	Brisbane Associated Friendly Societies' Medical Institute. Mount Isa Mines. Toowoomba Associated Friendly Societies' Medical Institute. Chillagoe Hospital. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL are advised, in their own interests, to submit a copy of their agreement to the Council before signing.
SOUTH AUSTRALIAN: Secretary, 207, North Terrace, Adelaide.	All Lodge Appointments in South Australia. All Contract Practice Appointments in South Australia.
WESTERN AUSTRALIAN: Honorary Secretary, 65, Saint George's Terrace, Perth.	All Contract Practice Appointments in Western Australia.
NEW ZEALAND (Wellington Division): Honorary Secretary, Wellington.	Friendly Society Lodges, Wellington, New Zealand.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

All communications should be addressed to "The Editor," THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: MW 2651-2.)

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